Suayib Yalcin
Philip A. Philip
Editors

Textbook of Gastrointestinal Oncology

Springer

Textbook of Gastrointestinal Oncology

Suayib Yalcin • Philip A. Philip
Editors

Textbook of Gastrointestinal Oncology

Springer

Editors
Suayib Yalcin
Department of Medical Oncology
Hacettepe University Institute of Cancer
Sihhiye, Ankara
Turkey

Philip A. Philip
Department of Oncology
Barbara Ann Karmanos Cancer Institute
Detroit, MI
USA

ISBN 978-3-030-18888-7 ISBN 978-3-030-18890-0 (eBook)
https://doi.org/10.1007/978-3-030-18890-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Including a wide range of malignant tumors, gastrointestinal cancers as a group form the second most prevalent cancers worldwide. Recently, significant progress has been observed in our understanding of the genetics, the epigenetics, and the biology of these cancers. This progress, coupled with the advancements in the early diagnosis and treatment, resulted in survival prolongations in most of the cases.

We hope this *Textbook of Gastrointestinal Oncology* will be a valuable and an informative source concerning the principles and practices in gastrointestinal oncology. We tried to cover all practice areas, such as pathology, radiological imaging, and interventions, and focused chapters on epidemiology, biology and genetics, staging, and multidisciplinary management of each of the specific gastrointestinal cancers. In addition to disease-oriented chapters, originating from sites spanning from the esophagus to the anus, hepatobiliary system, and pancreas, non-anatomic subjects such as palliative care, research issues, and modern imaging and interventional radiology techniques are also addressed. Information on translational science that is useful in the decision-making process is also given in the related chapters.

The comprehensive coverage with well-structured chapters makes this book a useful evidence-based reference for practitioners wishing to gain a greater understanding of the principles of diagnosis and management of patients with gastrointestinal cancers. The chapters are written by a selective group of international authors who are mostly recognized experts in their fields. The authors resemble the multidisciplinary management of gastrointestinal cancers. Besides medical oncologists, radiation oncologists, surgeons, gastroenterologists, pathologists, and nuclear medicine specialists, genetic experts, urologists, gynecologists, pediatricians, and nutritionists all contributed to the book.

We believe this book will be a valuable guide for oncologists, surgeons, gastroenterologists, and primary care providers looking for the latest and best information on how to deal with a patient who has a gastrointestinal cancer. We hope as our knowledge of the disease evolves, the book will also evolve in order to reflect the developments in the science in gastrointestinal cancer.

Sihhiye, Ankara, Turkey — Suayib Yalcin
Detroit, MI, USA — Philip A. Philip

Contents

1 **Global Epidemiology of Gastrointestinal Cancers** 1
Ömer Dizdar and Saadettin Kılıçkap

2 **Pathological Evaluation, Classification, and Staging of Gastrointestinal Cancers** 13
Vinod B. Shidham

3 **Pathological Evaluation, Classification, and Staging of Colorectal Cancers** 37
Maryam Kherad Pezhouh and Elizabeth A. Montgomery

4 **Esophageal and Gastroesophageal Junction Tumors** 55
Ebru Cilbir and Suayib Yalcin

5 **Gastric Cancer** 73
Yung-Jue Bang, Do-Youn Oh, Han-Kwang Yang, Sang Gyun Kim, and Woo-Ho Kim

6 **Small Bowel and Appendix Cancers** 97
Astrid Belalcazar-Portacio, Walid L. Shaib, and Bassel F. El-Rayes

7 **Adjuvant Therapy for Colorectal Cancer** 109
Patrick Boland, Jun Gong, and Marwan Fakih

8 **Metastatic Colorectal Cancer** 135
Mohamed E. Salem, Benjamin A. Weinberg, Feras J. Abdul Khalek, Jasmin R. Desai, Eiran A. Warner, Marion L. Hartley, and John L. Marshall

9 **Treatment of Rectal Cancer** 161
Mehmet Artaç, Bassel F. El-Rayes, Suayib Yalcin, and Philip A. Philip

10 **Squamous Cell Carcinoma of the Anal Canal** 175
Shahab Ahmed, Cathy Eng, and Craig A. Messick

11 **Cholangiocarcinoma** 185
Daniel H. Ahn and Tanios Bekaii-Saab

12 **Gallbladder Cancer: Current and Emerging Therapies** 197
Maria Diab and Philip A. Philip

13 Hepatocellular Carcinoma 207
Sahin Lacin, Asif Rashid, Yun Shin Chun, Bruno Calazans Odisio, Eugene J. Koay, Reham Abdel-Wahab, and Ahmed O. Kaseb

14 Resectable and Borderline Resectable Pancreatic Cancer 235
Megan A. Stevenson, Sameer H. Patel, and Syed A. Ahmad

15 Treatment of Advanced Pancreatic Carcinoma 255
Anteneh Tesfaye and Philip A. Philip

16 Gastroenteropancreatic Neuroendocrine Tumors 269
George A. Fisher

17 Gastrointestinal Stromal Tumors 289
Neeta Somaiah, Ridhi Gupta, and Shreyaskumar R. Patel

18 Gastrointestinal Cancers in Children 311
M. Tezer Kutluk and Erman Ataş

19 Gastrointestinal Lymphomas 329
Alma Aslan, Serkan Akın, Taner Babacan, and Evren Özdemir

20 Palliative Care in the Patient with Gastrointestinal Malignancies 351
David J. Debono

21 Gastrointestinal Cancers and Thrombosis 367
Arnab Basu and Alok A. Khorana

22 Nutrition and Cachexia in Gastrointestinal Cancer Patients 379
Meltem Gülhan Halil, Mehmet Emin Kuyumcu, Ömer Dizdar, Zekeriya Ulger, and Suayib Yalcin

23 Management of Peritoneal Malignancies 395
Richard N. Berri and Jennifer M. Ford

24 Advances in Radiation Therapy for Gastrointestinal Cancers 421
Rachit Kumar, Lauren M. Rosati, and Joseph M. Herman

25 Imaging in Gastrointestinal Cancers 445
Ali Devrim Karaosmanoglu, Mehmet Ruhi Onur, and Ronald S. Arellano

26 Immunological Treatment in Gastrointestinal Cancers 465
Héctor Randhall Callata-Carhuapoma and Jesús García-Foncillas López

27 Novel Targeted Treatment Approaches in Pancreatic Cancer 479
Maria Diab, Muhammad Saad Hamid, Ramzi M. Mohammad, Philip A. Philip, and Asfar S. Azmi

28 Improving Clinical Trial Design in Gastrointestinal Oncology 493
Ajlan Atasoy and Murielle Mauer

29 Gastrointestinal Cancer Prevention: Diet, Lifestyle, and Therapeutic Prevention 509
Phu N. Tran and Jason A. Zell

30 The Expanding Role of Endoscopy in Tissue Acquisition and Therapeutic Interventions for Gastrointestinal and Neuroendocrine Malignancies 533
James J. Farrell

31 Role of Interventional Radiology in Management of Gastrointestinal Cancers and Neuroendocrine Tumors 551
Ali Devrim Karaosmanoglu, Mehmet Ruhi Onur, and Okan Akhan

32 Screening for Gastrointestinal Cancers 573
Fadi Antaki, Stephanie Judd, Ziad Kanaan, Suhag M. Patel, and Kirthi K. Lilley

33 Hereditary Gastrointestinal Cancers 595
Selvi Thirumurthi, Eduardo Vilar, and Patrick J. Lynch

34 Molecular Diagnostics and Genomic Profiling in Individualized Therapies of Gastrointestinal Cancers 613
Mandana Kamgar and W. Michael Korn

35 Preserving Fertility in Patients with Gastrointestinal Cancers 633
Didem Tunalı, Sule Yildiz Oğuz, Ugur Selek, Emre Balik, Senol Tonyali, Sertac Yazici, and Özgür Öktem

36 Pregnancy and Gastrointestinal Cancers 655
Irfan Cicin, Gulay Durmus Altun, Nermin Tuncbilek, Yavuz Atakan Sezer, and Ezgi Cisil Erdogan

37 Vaccination in Patients with a Gastrointestinal Cancer 663
Şehnaz Alp and Murat Akova

38 Symptom Management in Gastrointestinal Cancers 669
Tugba Yavuzsen, Nazli Kazaz, Özgür Tanriverdi, Tulay Akman, and Mellar P. Davis

Index 687

Contributors

Reham Abdel-Wahab, MD Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Feras J. Abdul Khalek, MD Department of Hematology and Medical Oncology, Peninsula Regional Medical Center, Salisbury, MD, USA

Syed A. Ahmad, MD Department of Surgery, Division of Surgical Oncology, Pancreas Disease Center, University of Cincinnati Cancer Institute, University of Cincinnati Medical Center, Cincinnati, OH, USA

Shahab Ahmed, MD Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Daniel H. Ahn, DO, MS Division of Hematology/Medical Oncology, Mayo Clinic, Phoenix, AZ, USA

Okan Akhan, MD Department of Radiology, Hacettepe University, School of Medicine, Sıhhiye, Ankara, Turkey

Serkan Akın, MD Department of Medical Oncology, Hacettepe University Institute of Cancer, Sihhiye, Ankara, Turkey

Tulay Akman, MD Department of Medical Oncology, Tepecik Education and Research Hospital, Izmir, Turkey

Murat Akova, MD Department of Infectious Diseases and Clinical Microbiology, Hacettepe University School of Medicine, Sihhiye, Ankara, Turkey

Şehnaz Alp, MD Department of Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine, Sihhiye, Ankara, Turkey

Gulay Durmus Altun, MD, PhD Department of Nuclear Medicine, Physiology, Trakya University Medical Faculty, Edirne, Turkey

Fadi Antaki, MD Division of Gastroenterology, Department of Medicine, John D. Dingell Veterans Affairs Medical Center and Wayne State University, Detroit, MI, USA

Ronald S. Arellano, MD Department of Radiology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Mehmet Artac, MD Department of Medical Oncology, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey

Alma Aslan, MD Department of Medical Oncology, Hacettepe University Institute of Cancer, Sihhiye, Ankara, Turkey

Erman Ataş, MD Department of Pediatrics, Division of Pediatric Oncology, University of Health Sciences, Gulhane Training and Research Hospital, Etlik/Kecioren, Ankara, Turkey

Ajlan Atasoy, MD European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium

Research and Development, Oncology Clinical Development, Bristol-Myers Squibb, Lawrenceville, NJ, USA

Asfar S. Azmi, MD, PhD Department of Oncology, Wayne State University School of Medicine, Karmanos Cancer Institute, Detroit, MI, USA

Taner Babacan, MD Department of Medical Oncology, Hacettepe University Institute of Cancer, Sihhiye, Ankara, Turkey

Emre Balik, MD Department of Surgery, Koc University School of Medicine, Sariyer, Istanbul, Turkey

Yung-Jue Bang, MD, PhD Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Arnab Basu, MBBS, MPH Department of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Tanios Bekaii-Saab, MD Division of Hematology/Medical Oncology, Mayo Clinic, Phoenix, AZ, USA

Astrid Belalcazar-Portacio, MD Department of Hematology and Medical Oncology, Northern Light Eastern Maine Medical Center, Lafayette Family Cancer Center, Brewer, ME, USA

Richard N. Berri, MD, FACS Surgical Oncology, Peritoneal Malignancies Program, Department of Surgery, Ascension, St. John Hospital, Grosse Pointe, MI, USA

Patrick Boland, MD Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Héctor Randhall Callata-Carhuapoma, MD Department of Oncology, University Hospital Fundacion Jimenez Diaz – Autonomous University of Madrid, Madrid, Spain

Yun Shin Chun, MD, FACS Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Irfan Cicin, MD Department of Medical Oncology, Trakya University, Edirne, Turkey

Ebru Çilbir, MD Department of Medical Oncology, Dışkapı Yıldırım Beyazıt Education and Research Hospital, Ankara, Turkey

Mellar P. Davis, MD, FCCP, FAAHPM Lerner School of Medicine, Case Western Reserve University, Palliative Care Department, Geisinger Medical Center, Danville, PA, USA

David. J. Debono, MD Oncology and Palliative Care Solutions, Anthem Inc., Bloomfield Hills, MI, USA

Jasmin R. Desai, MD Department of Hematology and Oncology, Florida Cancer Specialists, Orlando, FL, USA

Maria Diab, MD Department of Oncology, Karmanos Cancer Institute, Detroit, MI, USA

Ömer Dizdar, MD, MSc Department of Medical Oncology, Hacettepe University Cancer Institute, Altındağ, Ankara, Turkey

Bassel F. El-Rayes, MD Clinical Research, Department of Hematology and Medical Oncology, Emory University School of Medicine/Winship Cancer Institute of Emory University, Atlanta, GA, USA

Cathy Eng, MD Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Ezgi Cisil Erdogan, MD Department of Medical Oncology, Trakya University Medical Faculty, Edirne, Turkey

Marwan Fakih, MD Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

James J. Farrell, MD Yale Center for Pancreatic Disease, Interventional Endoscopy, Section of Digestive Disease, Yale University School of Medicine, New Haven, CT, USA

George A. Fisher, MD, PhD Department of Medical Oncology, Stanford University School of Medicine, Stanford, CA, USA

Jennifer M. Ford, MD Department of Surgery, Astria Regional Medical Center and Heart Institute, Yakima, WA, USA

Jesús García-Foncillas López, MD, PhD Department of Oncology, University Hospital Fundacion Jimenez Diaz – Autonomous University of Madrid, Madrid, Spain

Jun Gong, MD Division of Medical Oncology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Ridhi Gupta, MD Department of Hematology and Medical Oncology, Maine General Medical Center/Harold Alfond Center for Cancer Care, Augusta, ME, USA

Meltem Gülhan Halil, MD Department of Internal Medicine, Division of Geriatrics, Hacettepe University School of Medicine, Altındag, Ankara, Turkey

Muhammad Saad Hamid, MD Department of Oncology, Karmanos Cancer Institute, Detroit, MI, USA

Marion L. Hartley, PhD Department of Medical Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA

Joseph M. Herman, MD, MSc Department of Radiation Oncology & Molecular Radiation Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Stephanie Judd, MD Division of Gastroenterology, Department of Medicine, John D. Dingell Veterans Affairs Medical Center and Wayne State University, Detroit, MI, USA

Mandana Kamgar, MD, MPH Department of Hematology Oncology, Karmanos Cancer Institute, Detroit, MI, USA

Ziad Kanaan, MD, PhD Division of Gastroenterology, Department of Internal Medicine, Wayne State University, Detroit, MI, USA

Ali Devrim Karaosmanoglu, MD Department of Radiology, Hacettepe University, School of Medicine, Sıhhiye, Ankara, Turkey

Ahmed O. Kaseb, MD Department of GI Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Nazli Kazaz, MD Department of Medical Oncology, Karadeniz Technical University, Kanuni Training and Education Hospital, Trabzon, Turkey

Alok A. Khorana, MD, FACP, FASCO Gastrointestinal Malignancies Program, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

Saadettin Kılıçkap, MD, MSc Department of Medical Oncology, Hacettepe University Cancer Institute, Altındağ, Ankara, Turkey

Sang Gyun Kim, MD, PhD Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul, Republic of Korea

Woo-Ho Kim, MD, PhD Department of Pathology, Molecular Pathology Center, Seoul National University Hospital, Seoul, Republic of Korea

Eugene J. Koay, MD, PhD Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

W. Michael Korn, MD Caris Life Sciences, Phoenix, AZ, USA

Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA, USA

Rachit Kumar, MD Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

University of Arizona, College of Medicine – Phoenix, Tucson, AZ, USA

Banner Thunderbird Medical Center, Glendale, AZ, USA

Banner MD Anderson Cancer Center, Gilbert, AZ, USA

M. Tezer Kutluk, MD, PhD, FAAP Department of Pediatrics, Division of Pediatric Oncology, Hacettepe University Faculty of Medicine & Cancer Institute, Hacettepe University Oncology Hospital, Yenişehir, Ankara, Turkey

Mehmet Emin Kuyumcu, MD Department of Internal Medicine, Division of Geriatrics, Hacettepe University School of Medicine, Altındag, Ankara, Turkey

Sahin Lacin, MD Department of Medical Oncology, Hacettepe Üniversitesi Sıhhiye Yerleşkesi, Altındağ, Ankara, Turkey

Kirthi K. Lilley, MD Division of Gastroenterology, Department of Medicine, John D. Dingell Veterans Affairs Medical Center and Wayne State University, Detroit, MI, USA

Patrick J. Lynch, JD, MD Department of Gastroenterology, Hepatology and Nutrition, University of Texas MD Anderson Cancer Center, Houston, TX, USA

John L. Marshall, MD The Ruesch Center for the Cure of GI Cancers, Department of Hematology and Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA

Murielle Mauer, MSc, PhD Department of Statistics, European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium

Craig A. Messick, MD Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Ramzi M. Mohammad, PhD Department of Oncology, Gastrointestinal Cancer Research, Wayne State University School of Medicine, Karmanos Cancer Institute, Detroit, MI, USA

Elizabeth A. Montgomery, MD Department of Pathology, Johns Hopkins University, Baltimore, MD, USA

Bruno Calazans Odisio, MD Department of Interventional Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Sule Yildiz Oğuz, MD Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, and Comprehensive Cancer Care and Fertility Preservation Programs, Koc University School of Medicine, Topkapi, Istanbul, Turkey

Do-Youn Oh, MD, PhD Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Özgür Öktem, MD Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, and Comprehensive Cancer Care and Fertility Preservation Programs, Koc University School of Medicine, Topkapi, Istanbul, Turkey

Mehmet Ruhi Onur, MD Department of Radiology, Hacettepe University, School of Medicine, Sıhhiye, Ankara, Turkey

Evren Özdemir, MD Department of Medical Oncology, Hacettepe University Institute of Cancer, Sihhiye, Ankara, Turkey

Sameer H. Patel, MD Department of Surgery, Division of Surgical Oncology, University of Cincinnati Medical Center, Cincinnati, OH, USA

Shreyaskumar R. Patel, MD Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Suhag M. Patel, MD Division of Gastroenterology, Department of Medicine, Unity Point Health, Allen Hospital, Waterloo, IA, USA

Maryam Kherad Pezhouh, MD, MSc Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Philip A. Philip, MD, PhD, FRCP, FABC Department of Oncology, Department of Pharmacology, Wayne State University, Karmanos Cancer Institute, Hudson-Webber Cancer Research Center, Detroit, MI, USA

Department of Oncology, Department of Pharmacology, Wayne State University School of Medicine, Karmanos Cancer Institute, Hudson-Webber Cancer Research Center, Detroit, MI, USA

Department of Oncology, Department of Pharmacology, Wayne State University, Karmanos Cancer Institute, Detroit, MI, USA

Asif Rashid, MBBS, PhD Department of Pathology, Division of Pathology/Lab Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Lauren M. Rosati, BS Department of Radiation Oncology & Molecular Radiation Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Mohamed E. Salem, MD Department of Oncology, Levine Cancer Institute-Concord, Concord, NC, USA

Ugur Selek, MD Department of Radiation Oncology, Koc University School of Medicine, Sariyer, Istanbul, Turkey

Yavuz Atakan Sezer, MD Department of General Surgery, Trakya University Medical Faculty, Edirne, Turkey

Walid L. Shaib, MD Department of Hematology and Medical Oncology, Emory University, Winship Cancer Institute, Atlanta, GA, USA

Vinod B. Shidham, MD, FRCPath, FIAC Department of Pathology, Karmanos Cancer Center, Wayne State University School of Medicine, & Detroit Medical Center, Detroit, MI, USA

Neeta Somaiah, MD Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Megan A. Stevenson, MD Department of Surgery, Division of Surgical Oncology, University of Cincinnati Medical Center, Cincinnati, OH, USA

Özgür Tanriverdi, MD Department of Medical Oncology, Mugla Sitki Kocman University Faculty of Medicine, Menteşe, Mugla, Turkey

Anteneh Tesfaye, MD Department of Oncology, Karmanos Cancer Institute, Detroit, MI, USA

Selvi Thirumurthi, MD, MS, FASGE, FACG Department of Gastroenterology, Hepatology and Nutrition, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Senol Tonyali, MD Department of Urology, Turkiye Yuksek Ihtisas Training and Research Hospital, Altındag, Ankara, Turkey

Phu N. Tran, MD Department of Hematology/Oncology, Genesis Healthcare System, Genesis Cancer Services, Zanesville, OH, USA

Didem Tunalı, MD Department of Internal Medicine, Division of Medical Oncology, Koc University School of Medicine, Topkapı, Istanbul, Turkey

Nermin Tuncbilek, MD Department of Radiology, Trakya University, Edirne, Turkey

Zekeriya Ulger, MD Department of Internal Medicine, Division of Geriatrics, Gazi University School of Medicine, Gazi University Hospital, Besevler, Ankara, Turkey

Eduardo Vilar, MD, PhD Department of Clinical Cancer Prevention; Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Eiran A. Warner, MD Department of Hematology/Oncology, Henry Ford Health System, Jackson, MI, USA

Benjamin A. Weinberg, MD Division of Hematology and Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA

Suayib Yalcin, MD Department of Internal Medicine, Division of Medical Oncology, Hacettepe University School of Medicine, Institute of Cancer, Altındağ, Ankara, Turkey

Han-Kwang Yang, MD, PhD, FACS Department of Surgery, Gastric Cancer Center, Seoul National University Hospital, Seoul, Republic of Korea

Tugba Yavuzsen, MD Department of Internal Medicine, Division of Medical Oncology, Dokuz Eylul University Faculty of Medicine, Balcova, Izmir, Turkey

Sertac Yazici, MD Department of Urology, Hacettepe University School of Medicine, Altındağ, Ankara, Turkey

Jason A. Zell, DO, MPH, MS Division of Hematology/Oncology, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, UC Irvine Medical Center, Orange, CA, USA

Global Epidemiology of Gastrointestinal Cancers

1

Ömer Dizdar and Saadettin Kılıçkap

Epidemiology of Gastrointestinal Tumors

The global cancer burden tends to increase. Increases in life expectancy, both in more- and less-developed countries, as well as growing population numbers are very important reasons for the increasing cancer incidence. However, lifestyle behaviors including smoking, physical inactivity, poor diet, and reproductive changes may also cause the increased cancer burden, especially in low-income and middle-income countries.

Worldwide, approximately 14 million new cancer cases and more than eight million cancer deaths were estimated in 2012 [1]. In males, the most common cancers in men are lung and prostate cancers. However, the total incidence of gastrointestinal (GI) system tumors—such as stomach, colorectal, and hepatocellular carcinoma—is higher than the lung and prostate cancer. In females, however, stomach and colorectum cancers are the most frequently diagnosed gastrointestinal system cancers.

In this section, we provide epidemiology and risk factors for GI cancers.

Esophageal Cancer

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer-related death in the world [1]. Around 80% of the cases worldwide occur in developing countries. The prognosis is poor, and the 5-year survival rate ranges from 15% to 25% [2]. About 456,000 new esophageal cancer cases and 400,000 deaths were estimated in 2012 worldwide [3]. The frequency (Fig. 1.1) varies according to geographical regions. The incidence rates are the highest in Eastern Asia (the age-standardized incidence: 11.0/100,000) and Southern Africa (5.9/100,000). However, the lowest rates are found in Western Africa (0.8/100,000). The incidence of esophageal cancer is 3 times higher in males than females. The age-standardized incidence rates were estimated to be 9.0 in males and 3.1 per 100,000 in females in 2012 [3].

There are two different histological types of esophageal cancer: squamous cell cancer (SCC) and adenocarcinoma. Squamous cell cancer of the esophagus usually occurs in the upper two-thirds of the esophagus, and adenocarcinoma seen in the distal third of the esophagus. Esophageal squamous cell carcinoma is the predominant histological type in the world. The frequency of esophageal squamous cell cancer is the highest in the region called the "Asian Esophageal Cancer Belt" that encompasses areas such as Turkey, Iran, Kazakhstan, and northern and central China [4–6]. In the Asian Esophageal Cancer Belt, 90% of cases are squamous cell histology. The incidence of esophageal cancer is estimated to be more than 100 cases/100,000 person-years in this area. The main risk factors of SCC of the esophagus include poor nutritional status, drinking beverages at high temperatures, smoking, alcohol, infection with human papillomavirus (HPV), and low intake of vegetables and fruits.

In developed countries such as the United States, and in Western Europe, adenocarcinoma is the most common subtype of esophageal carcinoma [2]. The incidence of esophageal adenocarcinoma has increased from 5.76 to 8.34 cases/100,000 person-years in the United States in the last 30 years. However, the incidence has been increasing rapidly in European countries in the last 5 years [2]. The mortality rates parallel with incidence rates in each country and tend to increase [3]. The major risk factors include obesity, Barrett's esophagus, smoking, low intake of fruits and vegetables, and gastroesophageal reflux disease (GERD) [2, 7].

Ö. Dizdar (✉) · S. Kılıçkap
Department of Medical Oncology, Hacettepe University Cancer Institute, Altındağ, Ankara, Turkey
e-mail: omer.dizdar@hacettepe.edu.tr

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_1

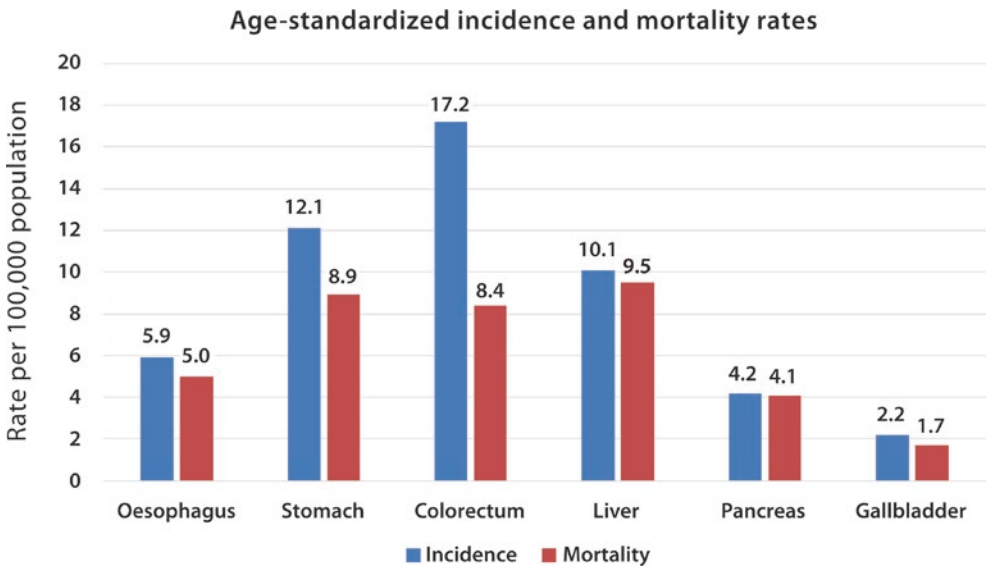


Fig. 1.1 Incidence and mortality rates of gastrointestinal tumors

Gastric Cancer

Gastric cancer is one of the most common causes of cancer-related death in the world and accounts for 8.8% of all cancer-related deaths [1]. The age-standardized mortality rate of stomach cancer worldwide is 8.9 per 100,000 persons. The highest mortality rates are in Eastern Asia (14.3/100,000) and the lowest rates in Northern America (2.1/100,000).

Gastric cancer is characterized by its predominance in males. Men are affected 2 to 3 times more often than women (12.3 per 100,000 years vs. 6.0 per 100,000 years) [8]. The disease shows regional variations between and within countries. Incidence of gastric tumor increases with age. At presentation, most gastric cancer patients are diagnosed with an advanced disease, with a 5-year survival rate lower than 30% [9, 10]. In the United States, the overall 5-year survival has been improved from 15% to 29% over the last 30 years [11]. However, survival rates are higher in Japan compared to other countries due to effectiveness of screening programs.

Although incidence of gastric cancer has decreased during last 2 decades, it is still the fourth most common cancer and the second leading cause of cancer deaths worldwide [12–14]. More than 950,000 new gastric cancers and 700,000 deaths were estimated in 2012. The highest incidence rates have been reported in Eastern Asia such as Korea, Japan, Mongolia, and China; Eastern Europe; and Southern America, with 24.2/100,000 [1, 3]. For example, the annual age-standardized gastric cancer incidence rates per 100,000 in men are 65.9 in Korea versus 3.3 in Egypt [15].

In these countries, accounting for approximately 50% of all cases of gastric cancer worldwide, distal tumors usually occur more frequently and are associated with the prevalence of *Helicobacter pylori* infection [16, 17]. However, other risk factors for distal gastric tumor include dietary patterns and nutritional habits. Recently, a steady decline in distal gastric cancer incidence has been noted due to the decreased incidence of *H. pylori* infection and the increased use of salt-preserved foods, fresh fruits, and vegetables.

The lowest incidence of gastric tumors has been reported in Northern America (4.0/100,000) and Western Europe (6.3/100,000). In developed countries, proximal gastric tumors are the most commonly occurring gastric cancer. They are associated with obesity and GERD.

Adenocarcinoma is the most commonly occurring histology for gastric cancer. It accounts for 95% of all gastric tumors. Other histological types include squamous cell carcinoma, adenosquamous carcinoma, lymphoma, gastrointestinal stromal tumor, leiomyosarcoma, and neuroendocrine tumor.

Small Intestine

Although the small intestine is the longest part of the tubular digestive tract, it is a relatively rare location for the development of cancer, with a global incidence of less than 1.0 case per 100,000 population [18, 19]. Cancers of the small intestine or small bowel (SBC) are responsible for only 0.42% of total cancer cases and 2.3% of cancers of the digestive system in the United States [20]. The incidence of small intestine cancer is higher in North America, Western Europe, and Oceania than in Asia [19, 21]. Mortality from small intestine cancers is even lower in the United States, accounting for only 0.2% of the total cancer deaths. Men have higher incidence rates than women.

There are four histological types of small intestine cancer: adenocarcinomas, neuroendocrine tumors, gastrointestinal stromal tumors, and lymphomas. Neuroendocrine tumor is the most frequent histological type, with 35–42% of neoplasms in the small intestine. Most of the small intestine neuroendocrine tumors are located in the ileum [22].

Adenocarcinoma is the second most commonly observed histological type, with 30–40% of the small intestine [21, 22]. Most of the tumors located in the duodenum and the duodenal-jejunal junction are adenocarcinomas.

Colorectal Cancer

Colorectal cancer (CRC) is one of the most frequent cancers with approximately 1,360,000 new cases globally [23]. Worldwide, it is the second most common cause of cancer-related deaths. It is the third most common cause of cancer-related death in developed countries, while in developing countries it is the second. In the United States, it accounts for 9% of cancer-related deaths [11]. Colorectal cancer is more frequent and causes more deaths in men than in women. However, mortality rates of colorectal cancer have been decreased due to effective screening programs in some countries such as Italy and Israel [24].

It is the third most commonly diagnosed cancer in men and the second in women. The highest incidence rates are in Australia/New Zealand, Europe, and the United States. In the United States, 134,000 new cases were diagnosed in 2012 [23]. The age-standardized incidence rate is 40/100,000 in the European Union. However, the lowest incidence rates of colorectal cancer have been reported in some Mediterranean countries. Incidence of colorectal cancer decreased in the United States but increased in some European countries such as Finland and Norway in the last 30 years [1]. Over the past few decades, the incidence and mortality rates of cancers originating in the rectum are rising in adults under 50 years old [25–27].

The incidence of colorectal cancer increases with age. The frequency of colorectal cancer is lower under 40 years of age; the frequency is approximately 1/1200 for under than 40 years old but 1/25 for over 70 years old [28]. For this reason, screening for colorectal cancer is recommended in adults over 50 years of age. In higher-risk populations, such as patients with familial polyposis coli and Lynch syndrome, the screening must be started under 40 years of age.

The prognosis of patients with colorectal cancer has improved in the last few decades because of improvements in diagnostic and treatment strategies. The 5-year survival rate has reached 65% in developed countries [24, 29, 30]. In patients with stage I colorectal cancer, 5-year survival is 90%, but only 12% for those with metastatic disease [24].

Primary Liver Tumors

Primary liver cancer is one of the most commonly diagnosed malignancies. It is the fifth most frequent tumor worldwide; in 2012, the number of the liver cancers was estimated to be 780,000 [31]. According to the Surveillance, Epidemiology, and End Results (SEER) program data, 5-year survival is approximately 17% in the United States but is lower in low-income countries (approximately 10%) [32, 33]. Primary liver cancer is the second most common cancer-related death in both sexes worldwide [32]. In 2012, an estimated 745,000 deaths due to liver tumors occurred in the world. Liver cancers are much more common in men than in women.

There are several histological types of liver tumors such as hepatocellular carcinoma and angiosarcoma [34]. Hepatocellular carcinoma accounts for most of the primary liver tumors [35]. The frequency of hepatocellular carcinoma varies according to different geographical regions. Incidence of hepatocellular carcinoma is the highest in East and Southeast Asia and Northern and Western Africa [36]. China accounts for about 50% of the new cases and deaths [36]. In populations where the incidence of hepatocellular carcinoma is the highest, frequency of chronic infection with hepatitis B virus (HBV), which is recognized as a major risk factor for hepatocellular carcinoma, is very high. The age-standardized incidence rates for hepatocellular carcinoma are lower in Europe and the United States. But, the incidence has increased in these populations due to the increased hepatitis C virus (HCV) infection, higher alcohol consumption, and the increasing incidence of nonalcoholic steatohepatitis (NASH). In the United States, the incidence has risen from 2.6/00.000 to 8.6/100.000 over the last 30 years [37]. However, the age-standardized incidence rates have decreased in regions such as Japan and China where it used to be an endemic disease as a result of the effective vaccination against HBV and improved hygiene and sanitation [38]. It is noteworthy that mortality rates from hepatocellular carcinoma have declined for the last few decades in Europe [39, 40].

Cholangiocarcinoma

Cholangiocarcinoma, originating from the epithelial lining of the bile duct (intrahepatic and extrahepatic bile duct), is a relatively rare tumor compared to the other tumors of gastrointestinal system. It accounts for 3% of all gastrointestinal malignancies [41]. The incidence increases with age and shows a wide variation in different geographical regions. Its incidence is lower in adults under 40 years old. The incidence of cholangiocarcinoma is higher in Asian countries such as Thailand, where *Opisthorchis viverrini* infection is endemic, than in the Western World. In Thailand, the age-standardized incidence rate reaches 113/100,000 person-years in men and 50/100,000 in women [42]. At diagnosis, most patients have advanced stage [43–45]. The 5-year survival rate is approximately 10% [43–45].

Gallbladder Cancer

Gallbladder cancer is the most common and the most aggressive tumor of the biliary tract malignancies [46, 47], accounting for 80–95% of biliary tract cancers in the world [48]. Gallbladder cancer accounts for 0.5% of all gastrointestinal tumors, with less than 5000 new cases per year in the United States [49]. The incidence of gallbladder cancer is the highest in the Mapuche Indians of Chile (35 per 100,000 each year), closely followed by Hispanics and North American Native Americans. The incidence increases with age and is two- to sixfold higher in women than men [50]. Although mortality is declining in some developed countries such as the United States, Canada, and Australia, it is increasing in Chile and Japan. The 5-year survival rate of gallbladder cancer is about 5% [51].

Pancreatic Cancer

The age-standardized incidence rate of pancreatic cancer is about 5/100,000 in men and 3.6/100,000 in women according to GLOBOCAN 2012. In the United States, the incidence is estimated as 7.5% with 49,000 new cases [52]. The age-standardized mortality rate of pancreatic cancer has not changed in the last 30 years despite improvements in treatment. Pancreas cancer is responsible for about 7.0% of cancer-related mortality in the United States. Median survival of pancreatic cancer is approximately 6 months and the 5-year survival rate is still under 5% [53–56].

The most frequent histology of pancreas carcinoma is adenocarcinoma. However, the other histological types include adenocytic carcinoma and neuroendocrine tumor. Incidence of pancreatic neuroendocrine tumors is increasing because of improvements in diagnostic techniques and pathology. In the last 30 years, the incidence has increased from 1.2% to 5.0%. The overall survival of pancreatic neuroendocrine tumors is longer than adenocarcinoma even for advanced disease and may extend beyond 10 years in patients with low-grade tumors.

Risk Factors for Gastrointestinal Cancers

Tobacco and Alcohol

Tobacco use is one of the major contributing factors in the development of gastrointestinal cancers. Cigarette smoke is strongly associated with esophageal and pancreatic cancer but also involved in gastric and colorectal cancers. Up to two-thirds of squamous cell carcinomas of the esophagus in the United States are attributed to smoking [57]. Gastric cancer risk also increases with smoking, and the risk of both gastric and esophageal cancer is exponentially enhanced with alcohol consumption [58, 59]. It has been estimated that 25% of pancreatic cancers are associated with tobacco smoking [60]. Compared to nonsmokers, the relative risks of colorectal cancer were 1.06 (95% confidence interval [CI]: 1.03–1.08) for 5 pack-years, 1.11 (95% CI: 1.07–1.16) for 10 pack-years, 1.21 (95% CI: 1.13–1.29) for 20 pack-years, and 1.26 (95% CI: 1.17–1.36) for 30 pack-years [61]; and case control studies showed increased anal cancer risk [62]. Cancer risk is related to both duration and intensity of smoking and can be significantly diminished following smoking cessation in patients with esophagus SCC, gastric cancer, and pancreatic cancer, eventually falling almost to the level of nonsmokers [63–65].

Tobacco smoke contains many mutagenic and carcinogenic compounds, including polycyclic aromatic hydrocarbons, nitrosamines, other aromatic amines, and miscellaneous organic compounds. Particularly, N-nitroso compounds, which are present both in our diet and in cigarette smoke, are harmful to our gut. While nicotine itself is not carcinogenic, thousands of other carcinogens in tobacco smoke form covalent bonds with DNA, thus producing DNA adducts. These adducts result in mutations in critical genes of somatic cells [66]. While this is the major pathway of carcinogenesis, epigenetic pathways including tumor suppressor gene inactivation by promoter methylation also have a role in tobacco-induced carcinogenesis. Differences in metabolic activation processes of carcinogens and efficacy of DNA repair enzymes determine the probability of cancer development and partially explain the individual differences in cancer risk [67].

Alcohol is also a significant risk factor for gastrointestinal cancers, with upper gastrointestinal cancers and hepatocellular cancer having the highest risk. Even low level of intake is associated with increased risk. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, 10% and 3% of the incidence of total cancer was attributable to former and current alcohol consumption. Alcohol-attributable fractions were 44% and 25% for upper aerodigestive tract, 33% and 18% for liver, and 17% and 4% for colorectal cancer for men and women, respectively [68]. A recent meta-analysis, including 486,538 cancer cases, showed relative risks (RRs) for heavy drinkers compared with nondrinkers and occasional drinkers to be 5.13 for oral and pharyngeal cancer, 4.95 for esophageal squamous cell carcinoma, and 1.44 for colorectal cancer. Heavy drinkers also had a significantly higher risk of stomach (RR 1.21), liver (2.07), gallbladder (2.64), pancreas (1.19), and lung cancer (1.15) [69]. Hepatocellular carcinoma (HCC) is associated with alcohol use, particularly mediated by alcoholic cirrhosis. Heavy drinkers are particularly at high risk, while mild drinkers have little or no increase in the risk of HCC [70, 71]. The relationship between alcohol and colorectal cancer may be

modified by dietary intake of folate, amount of alcohol consumption, and gender [68, 72, 73]. For most cancer sites, no significant difference was found with cancer risk and type of alcoholic beverage.

Alcohol consumption is increasing rapidly in many parts of the world. In 1988, the International Agency for Research on Cancer (IARC) listed alcohol among the carcinogens for oral cavity and pharynx, esophagus, liver, and larynx. Colorectal cancer and female breast cancer were later added to the list in 2010 [74]. Acetaldehyde is the key intermediate in alcoholic fermentation and ethanol oxidation. Mutagenic amounts of acetaldehyde can be detected in saliva after ingestion of moderate doses of ethanol [75]. It is the most abundant carcinogenic compound of tobacco smoke [76, 77]. This is the reason why smokers have a much higher risk of cancer when alcohol consumption is also present. Other proposed mechanisms for alcohol-induced cancer include increased estrogen concentration (breast carcinogenesis), a role as solvent for tobacco carcinogens, production of reactive oxygen species and nitrogen species, and changes in folate metabolism. The risk of cancer among alcohol drinkers is modulated by genetic risk factors. Variations in genes encoding enzymes that metabolize alcohol or function in folate metabolism or DNA repair alter the susceptibility to carcinogenic effects of alcohol [78].

Cancer Susceptibility Syndromes

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease characterized by the presence of hundreds of early-onset colorectal adenomas. Extracolonic manifestations include osteomas, desmoid tumors, and congenital hypertrophy of the retinal pigment epithelium, epidermoid cysts, fibromas, and dental abnormalities. The risk of upper GI tract cancer including duodenal or periampullary carcinoma and gastric cancer is also increased, and follow colorectal cancer as a major cause of cancer deaths in patients with FAP [79]. Other associated malignancies are pancreatic and thyroid cancers, hepatoblastoma, and medulloblastoma, but cumulative lifetime risk is much lower (<1–2%) [80]. Germline mutation in the adenomatous polyposis coli (APC) gene located on chromosome 5q21-q22 is the genetic defect present. FAP accounts for 1% of all colorectal cancers. If untreated, colorectal cancer develops in 100% of the patients at the age of 40–45 years. Prophylactic colectomy is recommended to reduce cancer risk. Patients with attenuated FAP have a history of >20 but <100 colorectal adenomas. The risk for developing CRC is increased, but, in contrast to classic FAP, polyps develop later in life and the risk for developing extracolonic neoplasms or desmoid tumors is lower. Screening with annual flexible sigmoidoscopy or colonoscopy should be started at age 10–12 in classical FAP and with annual colonoscopic screening at age 20–25 in attenuated FAP [81].

MUTYH-associated polyposis (MAP) is an autosomal-recessive polyposis syndrome caused by biallelic mutations in the *MUTYH* gene. MAP is characterized with late-onset (fifth decade) polyposis and presence of 10–100 colorectal polyps, but CRC can also develop in the absence of colorectal polyposis [82]. Management is similar to that of classic FAP or attenuated FAP.

Lynch Syndrome

The Lynch syndrome—or hereditary non-polyposis colorectal cancer (HNPCC)—is an autosomal dominant syndrome caused by germline mutations in DNA mismatch repair genes, i.e., MLH-1, MSH-2, MSH-3, MSH-6, PMS-1, or PMS-2, or loss of expression of *MSH2* due to deletion in the *EPCAM* gene. HNPCC accounts for 2–3% of all colorectal cancer cases. Overall incidence is 1/400 and it is the most common cancer susceptibility syndrome. Lifetime risk of CRC is 30–70% [83]. Bonadona et al. reported a cumulative risk of CRC at age 70 in 38% of males and 31% in females with substantial variability by genotype. MSH6 mutation carriers had lower cumulative risk of CRC compared with MLH1 or MSH2 mutation carriers (12% vs. 41% and 48%, respectively) [84]. Patients typically develop colon cancer at a young age. Mismatch repair defect results in microsatellite instability. Polyps are rarely seen, and cancer develops more rapidly than sporadic cases, which necessitates more frequent screening. Colonoscopy every 1–2 years starting at age 20–25 or 5 years before the youngest case in the family is recommended [85]. The risk of endometrial, ovarian, renal pelvis, and gastric cancer is also increased in the Lynch syndrome.

Hereditary Breast-Ovarian Cancer Syndrome

Hereditary breast-ovarian cancer syndrome is inherited in an autosomal dominant fashion with high penetrance caused by germline mutations in BRCA1 and BRCA2 genes. Lifetime risk of breast and ovarian cancer is approximately 60% in BRCA1 mutation carriers [86]. Data from the Breast Cancer Linkage Consortium (BCLC) reported relative risks of pancreatic cancer of 2.26 in *BRCA1* mutation carriers and 3.51 in *BRCA2* mutation carriers. An increased risk was also observed for gallbladder and bile duct cancer (RR = 4.97; 95% CI = 1. 50–16.52) and stomach cancer (RR = 2.59; 95% CI = 1.46–4.61) in BRCA2 mutation carriers [87]. The overall pancreatic cancer risk is about 1% and 4.9% for *BRCA1* and *BRCA2* mutation carriers, respectively [88].

Other hereditary cancer syndromes associated with gastrointestinal cancers are summarized in Table 1.1.

Table 1.1 Hereditary cancer syndromes associated with gastrointestinal cancers

Syndrome	Associated gene(s)	Associated cancers
Lynch syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Colorectal, gastric, pancreatic, endometrial, ovarian, and renal pelvis cancer
Familial adenomatous polyposis, Gardner and Turcot syndromes	APC	Colorectal cancer, osteomas, desmoid tumors, brain tumors, medulloblastoma
Peutz Jeghers syndrome	LKB1/STK11	Hamartomatous polyps, gastric, pancreatic and small intestine cancers, lung and breast cancer
Li-Fraumeni syndrome	TP53	Breast cancer, sarcoma, brain tumors, adrenocortical cancer
Cowden syndrome	PTEN	Colon, thyroid, breast, and uterus cancers
Hereditary breast ovarian cancer syndrome	BRCA1, BRCA2	Breast, ovarian, pancreatic, gastric, and laryngeal cancer
MUTYH-associated polyposis	MUTYH	Colorectal cancer
Familial juvenile polyposis	BMPR1A, SMAD4	Colorectal and gastric cancer
Tylosis	TOC	Esophageal cancer
Hereditary diffuse gastric cancer	CDH1	Gastric cancer
Ataxia telangiectasia	ATM	Pancreatic cancer, gastric and biliary tract cancer

Viruses

Since the 1970s, it has been known that hepatitis B virus (HBV) and hepatitis C virus (HCV) are closely linked with hepatocellular carcinoma. Large epidemiological studies showed overlapping distribution with chronic hepatitis and HCC and prospective studies have shown a 100-fold increased risk of HCC associated with chronic HBV infection [89]. HBV is a DNA virus; it contributes both directly to liver carcinogenesis through genomic integration in the tumor cells and indirectly by stimulating cellular proliferation in response to immune-mediated injury, inflammation, and fibrosis [90]. The mechanism of HCV-induced HCC is less clear. HCV-induced HCC is correlated with the degree of inflammation, and inflammation seems to be a major carcinogenic driver rather than specific oncogene activation. The cumulative lifetime incidence of HCC for patients with HCV alone was found to be 24% for men and 17% for women [91]. For HBV, lifetime HCC risk is variable. Advanced age and male gender, high viral load, active viral replication, and HBV genotype C harbor a higher risk of HCC [92, 93]. HBV vaccination has reduced the prevalence of HBV infection and antiviral drugs have reduced the risk of liver disease and the development of HCC [94]. Nucleoside analogues improve recurrence-free survival and overall survival after curative resection of HCC [95]. Successful treatment of HCV has also been associated with a decreased risk of HCC.

Papillomaviruses are DNA viruses with more than 140 different phenotypes. A subset of papillomaviruses is associated with cervical cancer, oropharyngeal/tonsil cancer, anal cancer, and nonmelanoma skin cancer. The E6 and E7 proteins encoded by HPV contribute to malignant transformation in infected cells. HPV causes anal intraepithelial neoplasia, which then progresses to dysplasia and invasive cancer. HPV 16 and 18 are particularly associated with malignant transformation. Vaccination against HPV is now routinely recommended for both males and females initiating at age 11–12 years through 26 years.

Epstein-Barr virus (EBV) is best known as the cause of nasopharyngeal carcinoma and some types of lymphoma. Recent studies have shown that EBV genes are also expressed in gastric cancer. The investigators from The Cancer Genome Atlas (TCGA) project proposed a molecular classification dividing gastric cancer into four subtypes, and tumor positive for Epstein-Barr virus is one of the subtypes comprising 9% of gastric adenocarcinomas. These EBV-positive tumors displayed recurrent *PIK3CA* mutations, extreme DNA hypermethylation, and amplification of *JAK2*, *PD-L1*, and *PD-L2* [96]. EBV positivity was more frequent in young males and was associated with diffuse-type histology and proximal gastric involvement [97, 98]. Previous studies showed similar prognosis, but some studies showed a lower rate of lymph node involvement [99].

Bacteria and Microbiome

Helicobacter pylori

H. pylori is a Gram-negative spiral bacterium that has a role in the pathogenesis of gastric cancer and gastric MALT lymphoma. *H. pylori* infection increases the risk of distal gastric adenocarcinoma by two- to tenfold in different studies but only a minority of the individuals will develop gastric cancer because the interaction between genetic and environmental factors and different strains of the bacteria results in individual variability in the outcomes of the infection [100]. IARC declared *H. pylori* as group 1 human carcinogen for gastric adenocarcinoma in 1994. IARC also estimates that the percentage of gastric cancer attributable to *H. pylori* infection is 36% and 47% in developed and developing countries, respectively. The exact mechanism of carcinogenesis is not com-

pletely understood. The bacteria cause chronic active gastritis and atrophic gastritis, which are precursors of adenocarcinoma. Diversity in the genome of *H. pylori*, alterations in host immune response to *H. pylori*, subsequent apoptosis, proliferation and differentiation of gastric epithelial cells, further augmentation of the interactions by diet, particularly salted food intake, and bacterial overgrowth in hypochlorhydria may have a role in cancer development [101]. Eradication of *H. pylori* reduces the risk of gastric cancer [102]. Gastric malt lymphoma risk is also increased with *H. pylori* infection. The *H. pylori* strains that express cag A protein are specifically linked with the increased cancer risk. *H. pylori* eradication alone can induce tumor remission in some cases [103]. There are studies suggesting an association between *H. pylori* infection and colon cancer, pancreatic cancer, and biliary tract cancer but the evidence is not strong and remains controversial.

Other Bacteria

With the advances in metagenomics approaches that combine next-generation sequencing platforms with the computational analysis and assembly of targeted (16S ribosomal RNA hypervariable region) and random (whole-genome shotgun) DNA sequence reads and human microbiome project, the diversity of human colon microbiota has been characterized [104]. Human microbiome studies have revealed differences in the relative abundance of certain microbes in cancer cases compared with controls indicating a clear link between bacteria, inflammation, and colorectal cancer. Microbiota are relatively stable within an individual compared with our exposures to external agents. There is also minor microbial variation within a human individual over their lifespan and a healthy individual retains specific strains for extended periods of time [105]. Further studies have revealed associations between colon microbiota and colon cancer [106]. The species particularly suggested to increased risk are *Fusobacterium*, *Streptococcus bovis*, and *Escherichia coli* [107, 108]. Many studies showed *Fusobacterium* positivity in colon cancer tissue, adjacent mucosa, and even in metastases of colon cancer [109, 110]. Human cancer types in which microbiota changes have been observed include colorectal cancer, oral, esophageal, pancreatic, and gallbladder cancer [111]. Continuation of these studies and integration with epidemiology studies will result in further clarification of cancer pathogenesis and develop preventive measures [112]. These data may have implications in developing cancer prevention and treatment strategies through targeting GI microflora by diet, probiotics, and antibiotics.

Diet

There have been extensive epidemiological data on certain diets, individual nutrients, methods of preparation and preservation, and increased or reduced risk of gastrointestinal cancer. The evidence mainly comes from observational studies resulting in the lack of definitive conclusions. Fruit and vegetable consumption was found to be associated with lower risk of colorectal, pancreatic, gastric, and esophageal cancer [113]. Dose-response evaluation revealed that each increase of 100 g of intake/day of fruit (SRR, 0.95) and vegetables (SRR, 0.96) was associated with a decrease in risk of gastric cancer [114]. Similar reductions in risk are described for esophageal carcinomas [115]. The risk of Barret's esophagus, the precursor lesion of esophageal adenocarcinoma, is also decreased with increased fruit and vegetable intake [116]. Increasing variety of the types of fruits and vegetables also decreased the risk of gastric cancer [117]. Antioxidants, flavons, and other micronutrients in fruits and vegetables might account for the reduced risk through scavenging oxygen radicals and inhibiting other processes associated with carcinogenesis (adhesion, invasion, and migration).

High salt intake is associated with increased gastric cancer risk [118]. The association is dose-dependent. High salt concentration in the stomach leads to mucosal damage through synergic action with *H. pylori* infection and increases the effects of carcinogenic nitrates in food. Consequently, salt-preserved foods also increase the risk of gastric cancer.

Case-control studies showed increased risk of gastric and esophageal cancer with red meat consumption but cohort studies showed a weaker association [119]. Many studies have found a link between red meat or processed meat intake and colorectal cancer risk [120, 121]. Diets high in red and processed meats have also been linked with increased risk of pancreatic cancer in some studies [122]. Heterocyclic amines and polycyclic aromatic hydrocarbons generated during cooking at high temperatures (broiling, barbecuing) and nitrosamines derived by gut microbiome through nitrates from processed meat are hypothesized to cause cancer. Undercooked beef was also suggested to increase CRC risk through some bovine infectious factors [123]. Recently, after thoroughly reviewing the accumulated scientific literature, the World Health Organization (WHO) IARC Monographs program classified processed meat as *carcinogenic to humans* (Group 1), based on *sufficient evidence* in humans that the consumption of processed meat causes colorectal cancer. The consumption of red meat was classified as *probably carcinogenic to humans* (Group 2A), based on *limited evidence* that the consumption of red meat causes cancer in humans and *strong* mechanistic evidence supporting a carcinogenic effect.

Foods containing dietary fiber probably protect against colorectal cancer. Large epidemiological studies found lower risk of adenomas and CRC with fiber consumption; however, the data is not entirely consistent. Probably, the type of fiber is important in risk-reduction potential. Fiber from grains was suggested to be more protective [124]. Foods containing milk and calcium, garlic, foods containing vitamin D, as well

as fish also probably protect against colorectal cancer [125–127]. Foods containing sugar and animal fats may increase the risk of colorectal cancer [128].

Foods containing folate (but not folic acid supplements) probably protect against colorectal and pancreatic cancer [129–131]. More research is needed to confirm these findings.

Obesity and Physical Activity

Many epidemiological studies have shown increased risk of overall cancer, and some cancers particularly have higher risk, in overweight/obese individuals. Visceral obesity was found to confer higher risk compared with abdominal obesity [132]. In the United States, about 20% of all female cancer deaths and 15% of male cancer deaths are obesity-related [133]. Obesity is associated with increased risk of esophageal cancer, colorectal cancer, hepatocellular cancer, pancreatic cancer, gastric cancer, and gallbladder cancer [134–136]. Increasing body mass index (BMI) further increased the risk. Uterine cancer, breast and ovarian cancer, prostate cancer, kidney cancer, non-Hodgkin's lymphoma, leukemia, and multiple myeloma are other non-GI cancers that have exhibited increased risk [137, 138]. Obesity is associated with a chronic inflammatory response characterized by abnormal and excessive cytokine production. The imbalance between pro-inflammatory cytokines (leptin, tumor necrosis factor-alpha [TNFa] or interleukin [IL]-6) and anti-inflammatory cytokines such as adiponectin may be involved in the carcinogenesis. This inflammatory state may contribute to the increased rate of cancers in obesity. The beneficial effects of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) on reducing colon cancer risk support this association. Obesity also increases gastroesophageal reflux, which is clearly associated with Barret's esophagus and esophageal adenocarcinoma. Dysregulation of insulin and insulin-like growth factor-1 signaling are other potential carcinogenic mechanisms linking obesity to cancer [134, 135].

Substantial evidence links reduced physical activity with an increased risk of colon, breast, and endometrial cancer [139–141]. Limited data also suggest a link between pancreatic and gastric cancer and physical activity [142–144]. A meta-analysis of 21 studies reported a 26–27% decreased risk of colon cancer among the most physically active compared with the least active individuals [145]. Physical activity also decreases the risk of recurrence in patients diagnosed with colon cancer. For example, a recent meta-analysis showed that physical activity before or after diagnosis reduces mortality from colorectal cancer [146]. The inverse association between physical activity and risk of colon cancer is independent of BMI [147]. Distinct or combined effects of physical activity and obesity on circulating hormones, adipocytokines, growth factors, insulin resistance, and immune function may be responsible for the beneficial effect of physical activity on cancer risk and mortality [141].

References

1. Cancer Research UK. Worldwide cancer statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer. Accessed 15 Aug 2018.
2. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381:400–12.
3. World Health Organization International Agency for Research on Cancer. Cancer fact sheets. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 17 Sept 2018.
4. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al., editors. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.
5. Islami F, Kamangar F, Aghcheli K, Fahimi S, Semnani S, Taghavi N, et al. Epidemiologic features of upper gastrointestinal tract cancers in Northeastern Iran. Br J Cancer. 2004;90:1402–6.
6. Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer. 2005;113:456–63.
7. Islami F, Kamangar F. Helicobacter pylori and esophageal cancer risk: a meta-analysis. Cancer Prev Res (Phila). 2008;1:329–38.
8. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893–1.
9. Suzuki R, Yamamoto E, Nojima M, Maruyama R, Yamano HO, Yoshikawa K, et al. Aberrant methylation of microRNA- 34b/c is a predictive marker of metachronous gastric cancer risk. J Gastroenterol. 2014;49:1135–44.
10. Bria E, De Manzoni G, Beghelli S, Tomezzoli A, Barbi S, Di Gregorio C, et al. A clinical-biological risk stratification model for resected gastric cancer: prognostic impact of Her2, Fhit, and APC expression status. Ann Oncol. 2013;24:693–701.
11. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
12. Bertuccio P, Chatenoud L, Levi F, Praud D, Ferlay J, Negri E, et al. Recent patterns in gastric cancer: a global overview. Int J Cancer. 2009;125:666–73.
13. Bosetti C, Bertuccio P, Malvezzi M, Levi F, Chatenoud L, Negri E, et al. Cancer mortality in Europe, 2005–2009, and an overview of trends since 1980. Ann Oncol. 2013;24:2657–71.
14. Peleteiro B, Severo M, La Vecchia C, Lunet N. Model-based patterns in stomach cancer mortality worldwide. Eur J Cancer Prev. 2013;23(6):524–31.
15. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomark Prev. 2010;19:1893–907.
16. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006;118:3030–44.
17. McCracken M, Olsen M, Chen MS Jr, Jemal A, Thun M, Cokkinides V, et al. Cancer incidence, mortality, and associated risk factors among Asian Americans of Chinese, Filipino, Vietnamese, Korean, and Japanese ethnicities. CA Cancer J Clin. 2007;57:190–205.
18. Hamilton SR, Aaltonen LA. World Health Organization classification of tumours. Pathology and genetics of tumours of the digestive system. Chapter 4. Lyon: IARC Press; 2000. p. 69–92.

19. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P. Cancer incidence in five continents Vol. IX. Lyon: IARC, IARC Scientific Publication, No. 160, 2007.
20. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59:225–49.
21. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249:63–7.
22. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. Ann Epidemiol. 2009;19:58–69.
23. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed 18 Mar 2016.
24. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62:220–41.
25. Austin H, Jane Henley S, King J, Richardson LC, Eheman C. Changes in colorectal cancer incidence rates in young and older adults in the United States: what does it tell us about screening. Cancer Causes Control. 2014;25:191–201.
26. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. Cancer Epidemiol Biomark Prev. 2009;18:1695–8.
27. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Rates of colon and rectal cancers are increasing in young adults. Am Surg. 2003;69:866–72.
28. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11–30.
29. Brenner H, Bouvier AM, Foschi R, Hackl M, Larsen IK, Lemmens V, et al.; EUROCARE Working Group. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. Int J Cancer. 2012;131:1649–58.
30. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. Lancet Oncol. 2010;11:165–73.
31. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC Cancer Base no. 11. Lyon: International Agency for Research on Cancer; 2013.. http://globocan.iarc.fr. Accessed 17 Sept 2018.
32. National Cancer Institute. Surveillance, epidemiology, and end results program. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. http://seer.cancer.gov/statfacts/html/livibd.html. Accessed 17 Sept 2018.
33. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
34. Boffetta P, Boccia S, La Vecchia C. Cancer of the liver and biliary tract. In: Boffetta P, Boccia S, La Vecchia C, editors. A quick guide to cancer epidemiology. Cham: Springer; 2014.
35. London WT, McGlynn KA. Liver cancer. In: Schottenfeld D, Fraumeni Jr J, editors. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006. p. 763–86.
36. El-Serag HB. Hepatocellular Carcinoma. N Engl J Med. 2011;365:1118–27.
37. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol. 2013;47(suppl):S2–6.
38. Center MM, Jemal A. International trends in liver cancer incidence rates. Cancer Epidemiol Biomark Prev. 2011;20:2362–8.
39. La Vecchia C, Lucchini F, Franceschi S, Negri E, Levi F. Trends in mortality from primary liver cancer in Europe. Eur J Cancer. 2000;36:909–15.
40. Bosetti C, Levi F, Boffetta P, Lucchini F, Negri E, La Vecchia C. Trends in mortality from hepatocellular carcinoma in Europe, 1980-2004. Hepatology. 2008;48:137–45.
41. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology. 2013;145:1215–29.
42. Mosconi S, Beretta GD, Labianca R, Zampino MG, Gatta G, Heinemann V. Cholangiocarcinoma. Crit Rev Oncol Hematol. 2009;69:259–70.
43. Shaib YH, Davila JA, Henderson L, McGlynn KA, El-Serag HB. Endoscopic and surgical therapy for intrahepatic cholangiocarcinoma in the United States: a population-based study. J Clin Gastroenterol. 2007;41:911–7.
44. Ustundag Y, Bayraktar Y. Cholangiocarcinoma: a compact review of the literature. World J Gastroenterol. 2008;14:6458–66.
45. Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut. 2012;61:1657–69.
46. Lai CH, Lau WY. Gallbladder cancer: a comprehensive review. Surgeon. 2008;6:101–10.
47. Zhu AX, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. Oncologist. 2010;15:168–81.
48. Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin. 2001;2001(51):349–64.
49. Pandey M. Risk factors for gallbladder cancer: a reappraisal. Eur J Cancer Prev. 2003;12:15–24.
50. Duffy A, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J Surg Oncol. 2008;98:485–9.
51. Levy AD, Murakata LA, Rohrmann CA Jr. Gallbladder carcinoma: radiologic-pathologic correlation. Radiographics. 2001;21:295–314.
52. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29.
53. Lau MK, Davila JA, Shaib YH. Incidence and survival of pancreatic head and body and tail cancers: a population-based study in the United States. Pancreas. 2010;39:458–62.
54. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371:1039–49.
55. Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971-2011: a population-based study. Lancet. 2015;385:1206–18.
56. Zell JA, Rhee JM, Ziogas A, Lipkin SM, Anton-Culver H. Race, socioeconomic status, treatment, and survival time among pancreatic cancer cases in California. Cancer Epidemiol Biomark Prev. 2007;16:546–52.
57. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005. Br J Cancer. 2009;101:855–9.
58. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2008;19:689–701.
59. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. Gut. 2010;59:39–48.
60. Fuchs CS, Colditz GA, Stampfer MJ, Giovannucci EL, Hunter DJ, Rimm EB, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch Intern Med. 1996;156:2255–60.
61. Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, et al. Meta-analyses of colorectal cancer risk factors. Cancer Causes Control. 2013;24:1207–22.
62. Frisch M. On the etiology of anal squamous carcinoma. Dan Med Bull. 2002;49:194–209.
63. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from

the international pancreatic cancer case-control consortium (Panc4). Ann Oncol. 2012;23:1880–8.
64. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010;102:1344–53.
65. González CA, Pera G, Agudo A, Palli D, Krogh V, Vineis P, et al. Smoking and the risk of gastric cancer in the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2003;107:629–34.
66. International Agency for Research on Cancer. Tobacco smoke and involuntary smoking. In: IARC monographs on the evaluation of carcinogenic risks to humans, vol. 83. Lyon: IARC; 2004. p. 53.
67. Schwartz AG, Prysak GM, Bock CH, Cote ML. The molecular epidemiology of lung cancer. Carcinogenesis. 2007;28:507–18.
68. Schütze M, Boeing H, Pischon T, Rehm J, Kehoe T, Gmel G, et al. Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. BMJ. 2011;342:d1584.
69. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015;112:580–93.
70. Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, et al.; Million Women Study Collaborators. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst. 2009;101:296–305.
71. Tanaka K, Hirohata T, Takeshita S, Hirohata I, Koga S, Sugimachi K, et al. Hepatitis B virus, cigarette smoking and alcohol consumption in the development of hepatocellular carcinoma: a case-control study in Fukuoka, Japan. Int J Cancer. 1992;51:509–14.
72. Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. Alcohol, low-methionine--low-folate diets, and risk of colon cancer in men. J Natl Cancer Inst. 1995;87:265–73.
73. Zhu JZ, Wang YM, Zhou QY, Zhu KF, Yu CH, Li YM. Systematic review with meta-analysis: alcohol consumption and the risk of colorectal adenoma. Aliment Pharmacol Ther. 2014;40:325–37.
74. International Agency for Research on Cancer. Alcohol consumption and ethyl carbamate. In: IARC monographs on the evaluation of carcinogenic risks to humans, vol. 96. Lyon: IARC; 2010.
75. Homann N, Jousimies-Somer H, Jokelainen K, Heine R, Salaspuro M. High acetaldehyde levels in saliva after ethanol consumption: methodological aspects and pathogenetic implications. Carcinogenesis. 1997;18:1739–43.
76. Weng MW, Lee HW, Park SH, Hu Y, Wang HT, Chen LC, et al. Aldehydes are the predominant forces inducing DNA damage and inhibiting DNA repair in tobacco smoke carcinogenesis. Proc Natl Acad Sci U S A. 2018;115:E6152–e61.
77. Salaspuro M. Acetaldehyde as a common denominator and cumulative carcinogen in digestive tract cancers. Scand J Gastroenterol. 2009;44:912–25.
78. Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol. 2006;7:149–56.
79. Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet. 1988;1:1149–51.
80. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138:2044–58.
81. Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, et al.; American Society of Clinical Oncology; European Society of Clinical Oncology. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology clinical practice guidelines. J Clin Oncol. 2015;33:209–17.
82. Grover S, Kastrinos F, Steyerberg EW, Cook EF, Dewanwala A, Burbidge LA, et al. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA. 2012;308:485–92.
83. Win AK, Young JP, Lindor NM, Tucker KM, Ahnen DJ, Young GP, et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol. 2012;30:958–64.
84. Bonadona V, Bonaïti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al.; French Cancer Genetics Network. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305:2304–10.
85. Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology clinical practice guidelines. J Clin Oncol. 2015;33:209–17.
86. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al.; EMBRACE. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. 2013;105:812–22.
87. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91:1310–6.
88. Thompson D, Easton DF. Breast cancer linkage C, cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94:1358–65.
89. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer. 1988;61:1942–56.
90. Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: from genes to environment. Nat Rev Cancer. 2006;6:674–87.
91. Huang YT, Jen CL, Yang HI, Lee MH, Su J, Lu SN, et al. Lifetime risk and sex difference of hepatocellular carcinoma among patients with chronic hepatitis B and C. J Clin Oncol. 2011;29:3643–50.
92. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al.; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295:65–73.
93. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al.; Taiwan Community-Based Cancer Screening Project Group. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med. 2002;347:168–74.
94. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol. 2010;53:348–56.
95. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. Hepatology. 2009;49:729–38.
96. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–9.
97. Camargo MC, Murphy G, Koriyama C, Pfeiffer RM, Kim WH, Herrera-Goepfert R, et al. Determinants of Epstein-Barr virus-positive gastric cancer: an international pooled analysis. Br J Cancer. 2011;105:38–43.
98. Murphy G, Pfeiffer R, Camargo MC, Rabkin CS. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. Gastroenterology. 2009;137:824–33.
99. van Beek J, zur Hausen A, Klein Kranenbarg E, van de Velde CJ, Middeldorp JM, van den Brule AJ, et al. EBV-positive gastric adenocarcinomas: a distinct clinicopathologic entity with a low frequency of lymph node involvement. J Clin Oncol. 2004;22:664–70.

100. Peek RM Jr, Blaser MJ. Helicobacter pylori and gastrointestinal tract adenocarcinomas. Nat Rev Cancer. 2002;2:28–37.
101. Sokic-Milutinovic A, Alempijevic T, Milosavljevic T. Role of Helicobacter pylori infection in gastric carcinogenesis: current knowledge and future directions. World J Gastroenterol. 2015;21:11654–72.
102. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? Ann Intern Med. 2009;151:121–8.
103. Zucca E, Bertoni F, Vannata B, Cavalli F. Emerging role of infectious etiologies in the pathogenesis of marginal zone B-cell lymphomas. Clin Cancer Res. 2014;20:5207–16.
104. Weinstock GM. Genomic approaches to studying the human microbiota. Nature. 2012;489:250–6.
105. Schloissnig S, Arumugam M, Sunagawa S, Mitreva M, Tap J, Zhu A, et al. Genomic variation landscape of the human gut microbiome. Nature. 2013;493:45–50.
106. Keku TO, Dulal S, Deveaux A, Jovov B, Han X. The gastrointestinal microbiota and colorectal cancer. Am J Physiol Gastrointest Liver Physiol. 2015;308:G351–63.
107. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012;22:299–306.
108. Boleij A, Tjalsma H. The itinerary of *Streptococcus gallolyticus* infection in patients with colonic malignant disease. Lancet Infect Dis. 2013;13:719–24.
109. Flanagan L, Schmid J, Ebert M, Soucek P, Kunicka T, Liska V, et al. Fusobacterium nucleatum associates with stages of colorectal neoplasia development, colorectal cancer and disease outcome. Eur J Clin Microbiol Infect Dis. 2014;33:1381–90.
110. Mima K, Nishihara R, Qian ZR, Cao Y, Sukawa Y, Nowak JA, et al. Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis. Gut. 2016 Dec;65(12):1973–80.
111. Schwabe RF, Jobin C. The microbiome and cancer. Nat Rev Cancer. 2013;13:800–12.
112. Bultman SJ. Emerging roles of the microbiome in cancer. Carcinogenesis. 2014;35:249–55.
113. Turati F, Rossi M, Pelucchi C, Levi F, La Vecchia C. Fruit and vegetables and cancer risk: a review of southern European studies. Br J Nutr. 2015;113(Suppl 2):S102–10.
114. Wang Q, Chen Y, Wang X, Gong G, Li G, Li C. Consumption of fruit, but not vegetables, may reduce risk of gastric cancer: results from a meta-analysis of cohort studies. Eur J Cancer. 2014;50:1498–509.
115. Li B, Jiang G, Zhang G, Xue Q, Zhang H, Wang C, et al. Intake of vegetables and fruit and risk of esophageal adenocarcinoma: a meta-analysis of observational studies. Eur J Nutr. 2014;53:1511–21.
116. De Ceglie A, Fisher DA, Filiberti R, Blanchi S, Conio M. Barrett's esophagus, esophageal and esophagogastric junction adenocarcinomas: the role of diet. Clin Res Hepatol Gastroenterol. 2011;35:7–16.
117. Jeurnink SM, Büchner FL, Bueno-de-Mesquita HB, Siersema PD, Boshuizen HC, Numans ME, et al. Variety in vegetable and fruit consumption and the risk of gastric and esophageal cancer in the European prospective investigation into cancer and nutrition. Int J Cancer. 2012;131:E963–73.
118. D'Elia L, Galletti F, Strazzullo P. Dietary salt intake and risk of gastric cancer. Cancer Treat Res. 2014;159:83–95.
119. Abnet CC, Corley DA, Freedman ND, Kamangar F. Diet and upper gastrointestinal malignancies. Gastroenterology. 2015;148:1234–1243 e4.
120. Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, et al. Meat consumption and risk of colorectal cancer. JAMA. 2005;293:172–82.
121. Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, et al. Meat, fish, and colorectal cancer risk: the European prospective investigation into cancer and nutrition. J Natl Cancer Inst. 2005;97:906–16.
122. Nitsche C, Simon P, Weiss FU, Fluhr G, Weber E, Gärtner S, et al. Environmental risk factors for chronic pancreatitis and pancreatic cancer. Dig Dis. 2011;29:235–42.
123. zur Hausen H. Red meat consumption and cancer: reasons to suspect involvement of bovine infectious factors in colorectal cancer. Int J Cancer. 2012;130:2475–83.
124. Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ. 2011;343:d6617.
125. Ngo SN, Williams DB, Cobiac L, Head RJ. Does garlic reduce risk of colorectal cancer? A systematic review. J Nutr. 2007;137:2264–9.
126. Aune D, Lau R, Chan DS, Vieira R, Greenwood DC, Kampman E, et al. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol. 2012;23:37–45.
127. Wu S, Feng B, Li K, Zhu X, Liang S, Liu X, et al. Fish consumption and colorectal cancer risk in humans: a systematic review and meta-analysis. Am J Med. 2012;125:551–9 e5.
128. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010;138:2029–2043 e10.
129. Song M, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. Gastroenterology. 2015;148:1244–60.e16.
130. Lin HL, An QZ, Wang QZ, Liu CX. Folate intake and pancreatic cancer risk: an overall and dose-response meta-analysis. Public Health. 2013;127:607–13.
131. Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, et al.; B-Vitamin Treatment Trialists' Collaboration. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet. 2013;381:1029–36.
132. Vainio H, Bianchini F. IARC handbooks of cancer prevention, volume 6, weight control and physical activity. Lyon: IARC Press; 2000.
133. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348:1625–38.
134. Tilg H, Moschen AR. Mechanisms behind the link between obesity and gastrointestinal cancers. Best Pract Res Clin Gastroenterol. 2014;28:599–610.
135. Mayne ST, Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. J Nutr. 2002;132:3467S–70S.
136. Aleman JO, Eusebi LH, Ricciardiello L, Patidar K, Sanyal AJ, Holt PR. Mechanisms of obesity-induced gastrointestinal neoplasia. Gastroenterology. 2014;146:357–73.
137. Pan SY, Johnson KC, Ugnat AM, Wen SW, Mao Y. Canadian Cancer Registries Epidemiology Research G, Association of obesity and cancer risk in Canada. Am J Epidemiol. 2004;159:259–68.
138. Rapp K, Schroeder J, Klenk J, Stoehr S, Ulmer H, Concin H, et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer. 2005;93:1062–7.
139. Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. Arch Intern Med. 2010;170:1758–64.
140. Borch KB, Weiderpass E, Braaten T, Jareid M, Gavrilyuk OA, Licaj I. Physical activity and risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) study. Int J Cancer. 2017;140:1809–18.
141. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. Lancet Oncol. 2017;18:e457–e71.

142. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med. 2016;176:816–25.
143. Behrens G, Jochem C, Schmid D, Keimling M, Ricci C, Leitzmann MF. Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. Eur J Epidemiol. 2015;30:279–98.
144. Wu L, Zheng W, Xiang YB, Gao YT, Li HL, Cai H, et al. Physical activity and pancreatic cancer risk among urban Chinese: results from two prospective cohort studies. Cancer Epidemiol Biomark Prev. 2018;27:479–87.
145. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104:1548–61.
146. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: a meta-analysis of prospective cohort studies. Int J Cancer. 2013;133:1905–13.
147. Friedenreich C, Norat T, Steindorf K, Boutron-Ruault MC, Pischon T, Mazuir M, et al. Physical activity and risk of colon and rectal cancers: the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomark Prev. 2006;15:2398–407.

Pathological Evaluation, Classification, and Staging of Gastrointestinal Cancers

2

Vinod B. Shidham

Introduction

Pathology as a diagnostic branch is an important pillar in the multidisciplinary management of most of the diseases including management of cancers. The insight provided by the microscopic features of any disease, *pathological evaluation of tissue,* is pivotal and an essential component in securing the best outcome in the multidisciplinary/multispecialty management of any cancer including gastrointestinal (GI) cancer.

GI cancer diagnosis involves multiple steps with various specialties including clinical examination for evaluating symptoms and signs, which guides the selection of an appropriate combination of imaging modalities, endoscopy, and various approaches for tissue diagnosis. The ultimate step is tissue diagnosis, the gold standard, with help of various biopsy methods. Sampling artifact due to missing of the actual pathology by random approach may be avoided by applying targeted methods guided by high-resolution endoscopy, such as different types of endomicroscopy in an effort to achieve in vivo histology-like real-time details (optical biopsy) [1–5].

Any of these methodologies has to conclude with appropriate expertise in ruling out various morphological mimickers by weeding out potential pitfalls in marching toward the correct diagnosis. Careful scrutiny of a variety of morphological features in the tissue specimens under examination is the most important step. Generally, the differential diagnosis involves a wide spectrum, spanning from reactive process at one end to various benign and malignant tumors at other end. If the morphological features are not sufficient enough to reach conclusive interpretation, a variety of ancillary tests may have to be applied. These ancillary tests include immunophenotyping by immunohistochemistry (IHC) or flow cytometry, fluorescence in situ hybridization/chromogenic in situ hybridization (FISH/CISH), cytogenetics, various molecular tests, electron microscopy, etc. Because it is easily adaptable to the routine anatomic pathology workflow using light microscopy, IHC is the most frequently used tool for evaluating diagnostic and prognostic immunomarkers. In addition, IHC has many other practical benefits, including feasibility to perform the immunostaining on archivable formalin-fixed paraffin-embedded (FFPE) tissue/cell-blocks. IHC slides can be stored like surgical pathology slides for future record. Ongoing refinement and availability of an ever-widening battery of immunomarkers along with increasing availability of multicolor immunostaining options for improved interpretation are continuously strengthening its ancillary status.

Thus, the interpretation of tissue for the diagnosis of any cancer is based on microscopic evaluation of morphological features with or without ancillary tests including immunophenotyping (immunohistochemistry/flow cytometry), cytogenetics, and variety of molecular pathology tests. Another component of interpretation is proper classification, which by itself, is an ongoing process based on increasing understanding with advances in the field of molecular pathology. Due to this, there are many tumor classifications for various cancers. However, depending on regional/local preferences and standard of practice, one or other classification is favored. In general, some classifications, such as the World Health Organization (WHO) classification [6] are favored over others. The tumors are generally classified based on their morphological features matching with its normal counterpart. This has been termed *histogenesis* (tissue of tumor origin). However, the preferred approach would be to consider the resemblance of a particular tumor to a particular type of normal tissue as its *differentiation* into that tissue type rather than as evidence of tissue of origin or *histogenesis*.

V. B. Shidham (✉)
Department of Pathology, Karmanos Cancer Center, Wayne State University School of Medicine, & Detroit Medical Center, Detroit, MI, USA
e-mail: vshidham@med.wayne.edu

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_2

Although not significantly important for all tumors, ***grading*** of tumor is an additional component of tissue diagnosis. Most of the approaches involve comparison of the tumor differentiation with the normal counterpart. Tumors with morphological resemblance closer to the normal spectrum would be "well differentiated" and the one lacking significant differentiation as "poorly differentiated," with "moderately differentiated" falling between the two extremes. This approach may be modified in some specific tumor/organ systems, such as in the application of mitotic figure count (proliferation status) and necrosis for grading neuroendocrine tumors (NET) [7] and gastrointestinal stromal tumors (GIST) [8, 9]. Ancillary tests such as KI-67 index may be applied for improved objectivity in tumor grading based on parameters related to proliferation [9a] are important factors to be considered for making treatment decisions. These features should be included in final pathology report under summary/synoptic report [10].

After tissue diagnosis and its proper classification, ***staging*** of that tumor has *prognostic significance* and is a critical component of any surgical pathology report on the resection specimen for proper clinical management. Currently, TNM (Tumor, Node, Metastasis) staging is the most widely practiced staging system. Based on various experiences, The American Joint Committee on Cancer (AJCC), in cooperation with the TNM Committee of the International Union Against Cancer (UICC), has incorporated these factors and developed a comprehensive TNM staging system, which is revised periodically [11–13, 15]. Each of the three components in TNM is given an incremental number as the tumor shows worsening features in that category. T (Tumor topography) is usually based on the size of tumor or the depth of the tumor invasion in tubular GI organs. Larger tumor size and/or deeper tumor invasion equates with a higher stage. N (extent of regional lymph node involvement) and M (evidence of distant metastasis) indicate the status regarding the spread of the tumor beyond the primary site as additional prognostic indicators. Depending on T, N, and M status, the AJCC has compiled various permutations and combinations into progressive groups from Stage 0 to Stage IV. In addition to TNM, other features such as Tumor deposits, Preoperative blood level of CEA, Tumor regresion score, Circumferential resection margin, Lymphovascular invasion, Perineural invasion, Microsatellite instability, KRAS and NRAS mutation, and BRAF mutation. Currently, this staging is one of the most important prognostic determinants and is important information in guiding the treatment plan [13]. Please see Table 2.1 in which "Colon carcinoma" is chosen as the organ system as an example for TNM staging [13]. The prognosis of higher stage cancer is poorer than lower stage cancers with shorter 5-year survival rates, even after curative resection [14].

Table 2.1 TNM staging based on AJCC eighth edition using *colon* as example (comparable approach with organ-specific details is applied for other tubular GIT) (see Fig. 2.5)

Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures

Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the Subserosa Mesentery Nonperitonealized pericolic or perirectal/mesorectal tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs (this category is not assigned by pathologists)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organ is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastasis

Table 2.1 (continued)

AJCC prognostic stage groups			
When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1–T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3–T4a	N1/N1c	M0	IIIB
T2–T3	N2a	M0	IIIB
T1–T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3–T4a	N2b	M0	IIIC
T4b	N1–N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois [15]. The original and primary source for this information is the *AJCC Cancer Staging Manual*, *Eighth Edition* (2017) published by Springer International Publishing

Table 2.2 Appendix: Comparative TNM staging according to AJCC applied to carcinoma *versus* neuroendocrine tumor [15]. (Note that for Appendix, in addition to TNM, grade of the tumor is also a consideration for staging of carcinoma, especially subcategorization of stage IV)

(a) Carcinoma	
Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intramucosal carcinoma; invasion of the lamina propria or extension into but not through the muscularis mucosae)
Tis(LAMN)	Low-grade appendiceal mucinous neoplasm confined by the muscularis propria. Acellular mucin or mucinous epithelium may invade into the muscularis propria T1 and T2 are not applicable to LAMN. Acellular mucin or mucinous epithelium that extends into the subserosa or serosa should be classified as T3 or T4a, respectively
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or the mesoappendix
T4	Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and/or directly invades adjacent organs or structures
T4a	Tumor invades through the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or serosa of the mesoappendix
T4b	Tumor directly invades or adheres to adjacent organs or structures

Table 2.2 (continued)

Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present, and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa or mesentery
N2	Four or more regional nodes are positive

Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits
M1b	Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
M1c	Metastasis to sites other than peritoneum

AJCC prognostic stage groups				
When T is…	And N is…	And M is…	And grade is…	Then the stage group is…
Tis	N0	M0		0
Tis(LAMN)	N0	M0		0
T1	N0	M0		I
T2	N0	M0		I
T3	N0	M0		IIA
T4a	N0	M0		IIB
T4b	N0	M0		IIC
T1	N1	M0		IIIA
T2	N1	M0		IIIA
T3	N1	M0		IIIB
T4	N1	M0		IIIB
Any T	N2	M0		IIIC
Any T	N0	M1a		IVA
Any T	Any N	M1b	G1	IVA
Any T	Any N	M1b	G2, G3, or GX	IVB
Any T	Any N	M1c	Any G	IVC

(b) Neuroendocrine tumor	
Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but less than or equal to 4 cm
T3	Tumor more than 4 cm or with subserosal invasion or involvement of the mesoappendix
T4	Tumor perforates the peritoneum or directly invades other adjacent organs or structures (excluding direct mural extension to adjacent subserosa of adjacent bowel), e.g., abdominal wall and skeletal muscle

(continued)

Table 2.2 (continued)

Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, and bone)
M1c	Both hepatic and extrahepatic metastases

AJCC prognostic stage groups			
When T is…	And N is…	And M is…	Then the stage group is…
T1	N0	M0	I
T1	N1	M0	III
T1	N0, N1	M1	IV
T2	N0	M0	II
T2	N1	M0	III
T2	N0, N1	M1	IV
T3	N0	M0	II
T3	N1	M0	III
T3	N0, N1	M1	IV
T4	N0	M0	III
T4	N1	M0	III
T4	N0, N1	M1	IV

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois [15]. The original and primary source for this information is the *AJCC Cancer Staging Manual, Eighth Edition* (2017) published by Springer International Publishing

Various organ systems have comparable methods to TNM staging, which may be modified in some cases based on the type of neoplasm. For example, TNM staging of the appendix for adenocarcinoma including goblet cell carcinoid (crypt cell carcinoma) is different than for neuroendocrine tumor (carcinoid) for the same organ (Table 2.2) [15].

The role of ***molecular pathology*** is evolving due to the ongoing introduction of a variety of targeted therapy for various GI cancers. The classical example is the role of *KIT* (CD117) in establishing the diagnosis of gastrointestinal stromal tumor (GIST) with evaluation for various KIT mutations related to the response to tyrosine kinase inhibitors such as Gleevec [16]. Other molecular tests are evolving continuously with an increasing role not only in treating GI cancer patients but also in monitoring/evaluating their relatives. An example includes evaluation for mismatch repair (MMR) genes for microsatellite instability (MSI), which is linked with the hereditary form of colorectal cancer in Lynch syndrome [17].

Most of this information is currently included as part of the final report on most of the definitive resections and some of the biopsies as per the College of American Pathologists (CAP) checklist for a particular tumor/organ [10, 18].

Pathological Evaluation

The standard of practice requires tissue diagnosis prior to initiation of treatment. Many lesions – both *benign* (including benign ulceration [usually due to ischemia or inflammatory processes, such as *Helicobacter pylori* infection in the stomach or cytomegalovirus infection in the colon], inflammatory conditions such as inflammatory bowel disease [Crohn's disease or ulcerative colitis], solitary rectal ulcer syndrome, and diverticular disease with mural stricturing, hamartomas, endometriosis, and adenomas) and *malignant* (including neuroendocrine tumors, lymphomas, mesenchymal tumors [e.g., GIST]), metastatic tumors with tendency for gastrointestinal tract metastases (e.g., melanomas), and malignancies growing into GI tract (GIT) from adjacent organs (e.g., cancers of the ovary, endometrium, urinary bladder, or prostate]) – *may clinically resemble GI carcinomas*. Due to this, it is critical to confirm the tissue diagnosis prior to definitive therapy as a standard of practice for the best outcome.

Tissue diagnosis and pathological evaluation may be achieved by various biopsy methods including fine-needle aspiration (FNA) biopsy (with its variants such as endoscopic ultrasound [EUS]-guided FNA, which is very important for evaluation of lesions of deeper organs such as the pancreas and other sites accessible through the tubular GI system) and other cytopathology methods including brushings, washings/lavages, and cyst aspirations. Surgical pathology approaches include endoscopic forceps biopsies/resection of small lesions such as polyps, core biopsy (including image-guided core biopsy), wedge biopsy (including laparoscopic biopsies), and ultimately resection specimens. Each of these approaches has benefits and limitations discussed briefly as follows.

Cytopathological Evaluation

Cytology has multiple advantages with the ability to evaluate excellent cytomorphological details (Fig. 2.1) over surgical pathology biopsy (Fig. 2.2). The principal mechanism by which the diagnostic material is retrieved by FNA facilitates selective suction of poorly cohesive neoplastic cells (Fig. 2.3) over supporting stroma, as compared to coring out of both stroma and tumor cells by core biopsy along the tract for that core (Fig. 2.3). FNA procedure samples a relatively wider area of the lesion because of the nature of the procedure in which the sampling FNA needle has to be moved back and forth in different directions in the tumor. Most of the sampled material is seen directly on the slides under scrutiny (in contrast to just a tiny fraction of the sampled surgical biopsy tissue as just a 4-micron thick tissue section) [19]. In addition to rapid turnaround time and lower cost, these specimens provide the opportunity to evaluate the cytomorphological features of tumor/lesion cells at a higher level of clarity with excellent nuclear details allowing precise diagnosis even with limited material (Fig. 2.1). In addition to the initial tissue diagnosis (Fig. 2.1), cytopathology contributes to

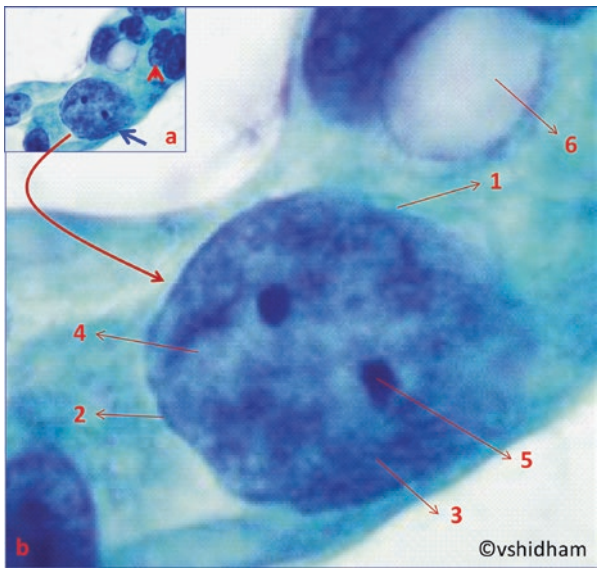


Fig. 2.1 Diagnostically crisp cytomorphological details in cytopathology samples (e.g., pancreatic ductal adenocarcinoma) (Pap stain – direct smear). (**a**) (inset): Cohesive group of neoplastic cells with sudden nucleomegaly. Variation in size of tumor nuclei: The difference in size between smallest (red arrowhead) and largest (blue arrow) nucleus in the group is at least 1:4. (**b**): 1. Large cell with high nuclear:cytoplasmic ratio; 2. irregular nuclear margin; 3. coarsely clumped irregularly distributed hyperchromatic chromatin; 4. parachromatin clearing; 5. nucleoli with irregular outlines; 6. cytoplasmic vacuoles with secretion (all these features collectively are consistent with adenocarcinoma)

the staging of many GI cancers such as TNM staging of colon cancer. Positivity of tumor cells in peritoneal fluid cytology is equivalent to the distant metastasis properly assigning a status of AJCC stage IV to these cases.

However, depending on a particular situation, invasion cannot be evaluated directly in the cytology specimens, although some indirect evidence such as tumor diathesis in the background with relatively higher cellularity may suggest that. Similarly, although some architectural details may be observed, it may not be comparable to that seen in surgical pathology (histopathology) tissue sections. Both these limitations could be overcome by using improved techniques for achieving best cellularity in cell-block sections from an adequately cellular cell-block [20, 21]. Recent advances for improving cellularity of cell-blocks allows maximum retrieval of diagnostic material in cell-block sections [19] [20a]. Cell-block also allows application of ancillary tests including IHC for differential diagnosis, for evaluation of prognostic markers, and for evaluating primary versus metastatic nature of the tumor. With the ever-increasing role of molecular tests, the cell-block is an excellent resource for many of these tests to be performed as indicated synchronously or at a later time on the archived FFPE cell-blocks. During on-site adequacy evaluation, it should be recommended to submit dedicated passes/material for cell-block preparation for future elective tests as clinically indicated. All these advantages of cell-blocks with

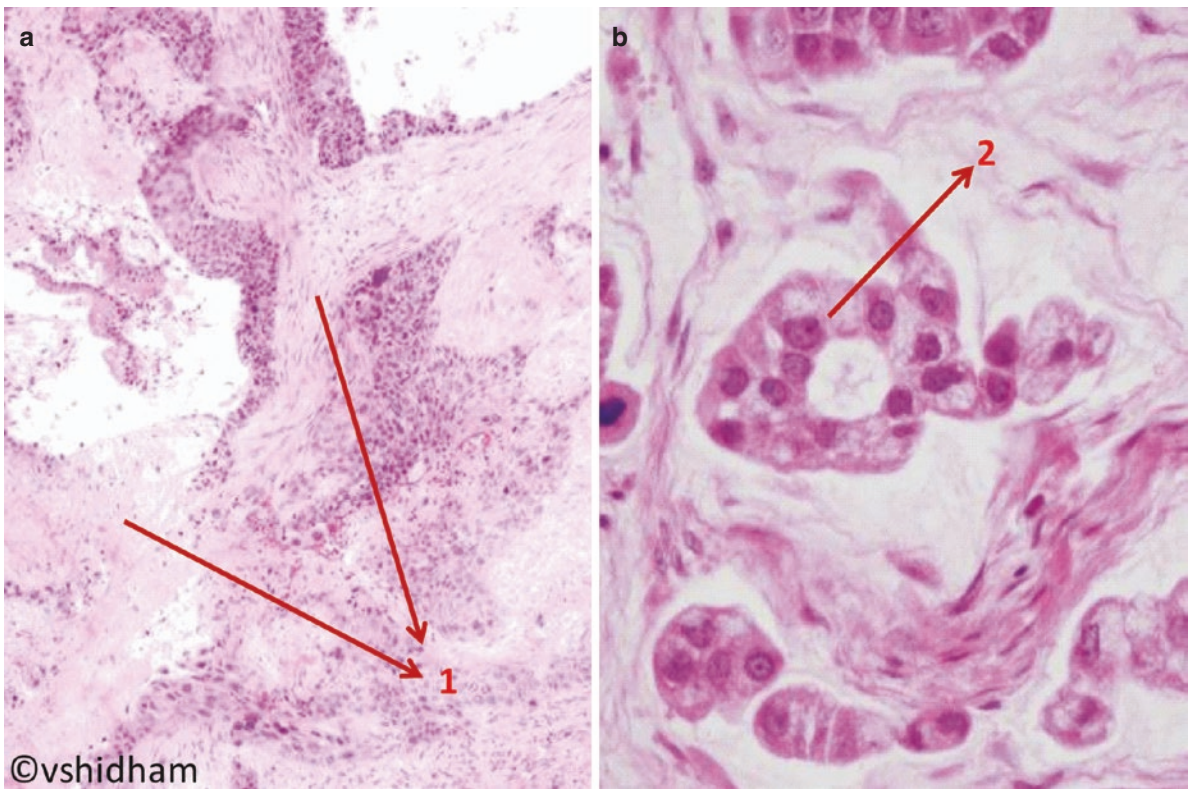


Fig. 2.2 Pancreatic adenocarcinoma (H&E) (**a**). Surgical pathology biopsy samples all tissue in the trajectory of the biopsy needle. Four-micron section of pancreatic ductal adenocarcinoma shows only fraction of the neoplastic epithelial component with predominance of stroma in section from tumors with predominance of desmoplastic stroma (compare with Fig. 2.3) (**b**). The morphology of individual tumor cells is relatively suboptimal as compared to cytology specimen (compare with Fig. 2.1). Similarly, the evaluation of sudden nucleomegaly is also relatively less dependable in surgical pathology sections

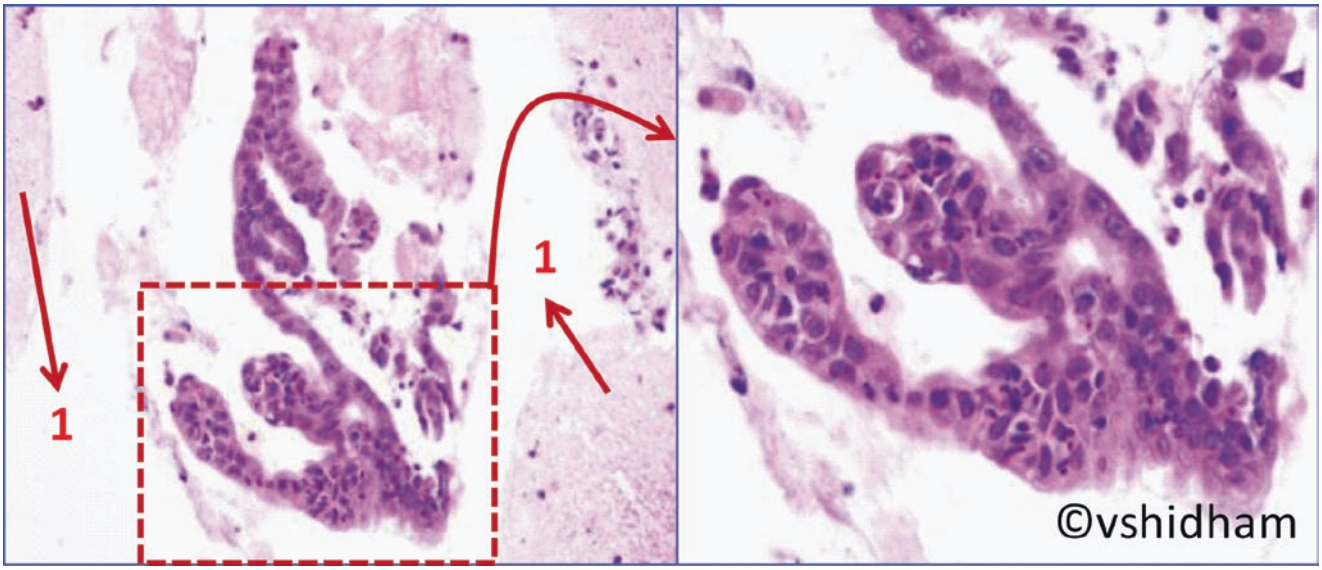


Fig. 2.3 Pancreatic adenocarcinoma (H&E). Cell-block section of FNA biopsy specimen (H&E stain). Note tumor with predominantly neoplastic epithelial component without significant proportion of stroma

recent advances are discussed in detail in the recent review article on CellBlockistry [21a].

Cytological approaches facilitate preoperative tissue diagnosis of lesions, especially those that otherwise may not be accessible with conventional biopsy due to complex locations (most of the pancreatic lesions) or due to potential risks of biopsy-associated complications such as needle tracking. However, due to the relative complexity in interpreting cytopathology material, the availability of expertise may be limited to some special centers.

Onsite adequacy evaluation is an important component to navigate the exact area to be sampled and provide real-time input for retrieval of adequate diagnostic material with triage feedback for appropriate supporting tests such as flow cytometry, microbiology cultures, and cytogenetics. The final goal of onsite adequacy evaluation is to achieve diagnostic material for unequivocal cytopathological interpretation, which for adenocarcinoma and other nonhematopoietic lesions is heavily dependent on evaluation of Papanicolaou (Pap) stained smears. Due to this, it is important to ensure retrieval of diagnostic material on the Pap-stained smears (instead of Diff-Quick [DQ]-stained smears), especially when only a suboptimal scant specimen could be available for final interpretation. In such cases, use of DQ stain initially for onsite adequacy may compromise the final interpretation especially if the lesion turns out to be a well-differentiated adenocarcinoma with scant material, leading to atypical/suspicious type suboptimal final report. Conventionally, wet-fixed smears are needed for Pap staining and air-dried counterpart for DQ staining. However, air-drying of all smears allows application of either Pap stain (after rehydration with post-fixation) or DQ stain electively [22]. Based on published study and long personal experience, using air-dried smears with routine availability of rapid Pap staining protocol during onsite adequacy evaluation is recommended for increasing the chances of final unequivocal cytopathological interpretation of most GI nonhematopoietic lesions [22].

Table 2.3 Cytopathological evaluation of GI lesions

Organ system/lesion	Procedure	Remark
Esophagus	Endoscopic brushing Others – such as: Abrasive balloon [23] Cytosponge in gelatin capsule [24]	Candida, viral cytopathic effect, Barrett's esophagus, dysplasia, carcinoma
Stomach	EUS-FNA	Deeper solid lesions; e.g., GIST
Pancreas	EUS-FNA	Cystic and solid lesions
Pancreatic duct	Endoscopic brushing	Dysplasia, carcinoma
Ampulla of Vater	Endoscopic brushing	Dysplasia, carcinoma
Bile duct	Endoscopic brushing	Dysplasia, carcinoma
Liver	Image-guided FNA	Solid (or cystic) lesions
Lesions – lymph nodes around/ adjacent to tubular GI	EUS-FNA	Cysts and solid lesions
Anal canal	Anal Pap (brushing)	Dysplasia/carcinoma

EUS endoscopic ultrasound, *FNA* fine-needle aspiration, *GIST* gastrointestinal stromal tumor, *GI* gastrointestinal

Commonly used approaches for cytological sampling of lesions in various organ systems are summarized in Table 2.3 [23, 24].

Surgical Pathological (Histopathological) Evaluation

Surgical pathological (histopathological) evaluation of lesions suspicious for cancer identified after clinical examination in concert with different imaging modalities and/or various endoscopic studies with suspicion for malignancy is another modality available in addition to cytopathological methods. Similar to cytopathological evaluation, the role of the biopsy is to distinguish benign lesions from clinically neoplastic mimickers and to rule out or rule in malignancy along with histological typing of the tumor.

Similar to cytopathological evaluation, a variety of approaches may be used to retrieve tissue for surgical pathological (histopathological) evaluation of suspicious lesions. The methodology may range from minimal representative sampling to total resection in various forms and may be categorized mainly into:

1. Diagnostic sampling
   A. Diagnostic biopsies (may be supported by guidance from onsite adequacy evaluation for precise sampling of the lesion by intra-procedural cytology smears)
      (a) Needle core biopsies
      (b) Endoscopic forceps biopsies
      (c) EUS-guided core biopsies
   B. Wedge biopsies
   C. Excisional biopsies
2. Therapeutic excisions
   A. Wide excisions, including endoscopic mucosal resections (EMR) [25]
   B. Radical resections

The major benefit with most of the surgical pathology specimens is the ability to evaluate the tissue architecture and invasion (Fig. 2.2). Even though FNA with good cell-block has numerous benefits as stated previously, there may be a tendency to prefer needle core biopsy over the relatively skill-dependent FNA procedure due to perceived ease in performing core biopsies. Generally, the cytopathological approach has a higher chance of diagnostic outcome as compared to core biopsies with small/tiny tissue for surgical pathology, especially for tumors with a tendency for sclerotic/desmoplastic stroma (e.g., pancreatic ductal carcinoma) [26, 27].

However, the final result with surgical pathology depends on a variety of factors including how the tissue is collected, from where it is collected, how it is fixed and processed, and the final quality of tissue sections with elective application of ancillary tests for final interpretation.

For diagnostic biopsies, it is important to sample the proper area of any lesion. For sampling ulcerated lesions and retrieving representative diagnostic material, the specimens should be taken from all 4 quadrants of the ulcer edge (e.g., for ulcerated carcinomas) and its base (e.g., for ulcerated lymphoma and sarcoma). The surface of the polypoid lesions would be the representative tissue. However, superficial biopsies such as from tubular gut or the ampulla of Vater, extrahepatic bile ducts, and pancreatic ducts may be limited by the difficulty in evaluating the invasion and its depth. For sampling obstructive lesions, an endoscope may not be negotiable and so may be difficult to biopsy. In such cases, brush cytology is an appropriate alternative. Some deeper lesions such as lymphomas, neuroendocrine tumors, GIST, and sarcomas usually have deeper submucosal mural growth pattern. Such lesions may be missed in superficial luminal biopsies and so, in this clinical situation, the same specific biopsy site should be sampled repeatedly to retrieve the representative deeper tissue. Tumors with extensive necrosis may not provide a sample with viable diagnostic component. In such cases, sampling multiple biopsies, especially from the periphery of the lesion, would enhance the possibility of sampling viable diagnostic tissue. In addition, core biopsies may not sample diagnostic material or if it samples diagnostic tissue, it may not be sufficient for precise grading of some lesions such as NETs and GIST. Calculation of Ki67 (MIB1) index (need at least 500 to 1000 tumor cell nuclei) and mitotic figure counting (need up to 50 high power fields) may not be precise on specimens with scant viable tumor components [7, 8].

Intraoperative Consult (Including Frozen Sectioning and Imprint/Scrape Cytology Smears)

The final management, especially resection, may need intra-procedural input to guide the surgical treatment. The most common indication is *evaluation of the resection margins* for the tumor. Other benefits of the intraoperative consult include triaging of the fresh specimen for ancillary studies such as cytogenetics, flow cytometry, microbiology culture, and ultrastructural (electron microscopic) studies as indicated based on preliminary morphological evaluation. Some of these ancillary tests may not be possible at a later stage once the tissue is fixed. It is important not to use frozen sections (FS) routinely just for the diagnosis, especially on tiny biopsies and tissues with predominance of fat. Performance of FS without considering this limitation may compromise the morphology required for optimal final interpretation, including interference with some studies such as elective IHC. In case the tissue diagnosis input is a must on such specimens, intra-procedural *imprint/scrape cytology smears* is a better option [27a].

Specimen Handling

For the best interpretation outcome, both cytopathology and surgical pathology specimens have to be collected, handled, and processed properly. All personnel associated in this process should be aware of limitations and precautions with

emphasis on coordination and communication between different entities involved in it for the best outcome. Compromisation may affect the integrity of the specimen needed for the best outcome. Improper fixative, inappropriate fixation time, or prolonged ischemic time (time from excision to putting the specimen in the fixative) may compromise the results of ancillary tests, especially the immunostaining pattern/immunophenotype.

Although *cytopathology specimens* have many benefits as mentioned previously, they also have many challenges due to the complexity in choosing an appropriate collection protocol [20]. Close collaboration with the cytopathology laboratory is needed to achieve the best outcome. The simplest approach would be to submit a fresh specimen to the cytopathology laboratory for immediate processing. Similarly, air-dried direct cytology smears allow more flexibility and may be processed for both Pap and Diff-Quik staining with multiple benefits [22]. If this is not possible, it should follow the protocol standardized for their particular laboratory/institution (Table 2.4) [20, 22].

Table 2.4 Cytopathology specimen submission protocols

Specimen	Specimen submission protocol	Processing
Brushing smear	**Direct smear** (need proper training to smear the specimen on slides) *Smears may be*: **Wet-fixed smear** (immersing the smears in 95% ethyl alcohol before any spread material dries on the slide)	**Papanicolaou (Pap) staining**
	Air-dried smear (the slide with spread specimen is allowed to dry quickly – preferably within 30 seconds)	**Pap staining –** after rehydration with post-fixation [22] **Romanowsky staining** (most commonly used is **Diff-Quik (DQ) staining**) May also be used for **other special stains** such as GMS stain for fungus, etc.
Brushing tip	Tip of the brush with sample is submitted in **cytology fixative** (such as *CytoLyt*® or other *liquid-based cytology (LBC) fixative* for methodologies such as Thinprep® or Surepath™ as recommended by the laboratory)	Direct smear from the sediment or Cytospins™ – both may be stained with Pap or DQ stain LBC smears (Thinprep® or Surepath™) for **Pap staining** Not suitable for cell-block, due to potential compromisation of IHC and other tests.
	In **isotonic medium** such as saline, RPMI, other isotonic such as IsotonicMediumS™ [20a] (should be submitted to cytopathology laboratory for immediate processing without delay – otherwise, the specimen integrity will be compromised)	Direct smear from the sediment or Cytospins™ – both may be stained with Pap or DQ stain LBC smears (Thinprep® or Surepath™) for **Pap staining** If enough sediment – it may be processed **for cell-block** with appropriate method depending on the cellularity of the brushing specimen
Washings/lavages	In **isotonic medium** such as saline, RPMI, other isotonic such as IsotonicMediumS™ [20a] (should be submitted to cytopathology laboratory for immediate processing without delay – otherwise, the specimen integrity will be compromised)	Direct smear from the sediment or Cytospins™ – both may be stained with Pap or DQ stain LBC smears (Thinprep® or Surepath™) for **Pap staining** If enough sediment – it may be processed **for cell-block** with appropriate method depending on the cellularity of the specimen
Serous effusions	Fresh (preferably 100 ml up to 1000 ml) (see reference [20], for more details)	Direct smear from the sediment or Cytospins™ – both may be stained with Pap or DQ stain LBC smears (Thinprep® or Surepath™) for **Pap staining** **For cell-block** with appropriate method depending on the cellularity of the specimen
Fine-needle aspiration (FNA) biopsy (with on-site adequacy evaluation and triage)	**Direct smear** (need proper training to smear the specimen on slides) *Smears may be*: **Wet-fixed smear** (immersing the smears in 95% ethyl alcohol before any spread material dries on the slide)	**Pap staining**
	Air-dried smear (the slide with spread specimen is allowed to dry quickly, preferably within 30 seconds)	**Pap staining –** after rehydration with post-fixation [20] **Romanowsky staining** (most commonly used is **Diff-Quik (DQ) staining**) May also be used for **other special stains** such as GMS stain for fungus, etc.
	Needle rinses in **isotonic medium** such as saline, RPMI, other isotonic such as IsotonicMediumS™ [20a] (should be submitted to cytopathology laboratory for immediate processing without delay – otherwise, the specimen integrity may be compromised). If needed needle rinses may be submitted directly in 10% formalin – but this part cannot be used for cytology preparations, but good for preparation of cell-block	Cytospins™ – both may be stained with Pap or DQ stain LBC smears (Thinprep® or Surepath™) for **Pap staining** **For cell-block** with appropriate method depending on the cellularity of the specimen

GMS Gomori's methenamine silver, *RPMI* Roswell Park Memorial Institute

Small surgical pathology specimens such as core/forceps biopsies in general can be submitted in 10% formalin. Large specimens may be submitted in 10% formalin or as fresh, but fresh specimens must be processed immediately for appropriate final outcome. Fresh unfixed specimen provides the benefit and flexibility of applying different protocols, but not without the risk of compromising tissue integrity if immediate processing cannot be guaranteed. Some specimens may need special attention with preliminary orientation and processing to avoid a sub-optimal outcome. A good example in this category is endoscopic mucosal resection (EMR) specimens. These specimens should be oriented and mounted by pinning onto a paraffin wax block or cork board before submitting in fixative prior to transportation to the laboratory [25].

Application of Various Ancillary Tests

Routine morphological evaluation may not be sufficient for reaching a definitive interpretation, especially with limited biopsy specimen, scantly cellular cytology specimen, or some lesions such as poorly differentiated tumors. Ancillary methods including immunohistochemistry, in situ hybridization (FISH and CISH), other molecular tests, ultrastructural studies (electron microscopy), or histochemistry may be indicated.

The most powerful and practical tool widely used currently is IHC. Other tools have relative limitations and are used sparingly. Electron microscopy needs planning from the beginning of the biopsy procedure when the tissue is still fresh, so that it is appropriately processed with special fixative (glutaraldehyde). In addition, it takes several days to obtain results and is labor intensive. Due to this, the role of electron microscopy has been decreasing steadily with ongoing refinement in IHC. Histochemistry may be performed for neutral and acidic mucins (adenocarcinoma), glycoproteins (adenocarcinoma or hepatocellular carcinoma), neurosecretory granules (neuroendocrine tumors), melanin (primary or metastatic melanoma), and other tumor cell products or associated proteins. But most of these are detected by IHC with better specificity and sensitivity even for detecting some organisms such as *Helicobacter pylori* in gastric biopsies, thus limiting the role of histochemistry in today's practice environment. However, histochemistry is still used for some indications such as for detection of various organisms such as fungi (Periodic acid–Schiff for fungus [PAS-F] and Gomori's methenamine silver [GMS] stain) or acid-fast organisms (various acid-fast bacillus [AFB] stains).

Immunohistochemical Assessment

An increasing number of antibodies that may be applied to FFPE tissue are continuously being added to the ever-expanding spectrum of diagnostic and prognostic immunomarkers. This has facilitated widespread application of immunohistochemistry [28, 29] in routine diagnostic pathology. However, for some lesions, such as lymphomas, there is preference for fresh tissue in isotonic medium for immunolabeling and evaluation by flow cytometry. Although immunophenotyping (either IHC or flow cytometry) is a very powerful tool, it is absolutely essential to understand that it is an ancillary tool and has to be used in the context of a carefully structured differential diagnosis with reference to the clinical details and morphological findings. There are many pitfalls with potential false positivity if this caveat is not taken into consideration. It may be applied for a variety of indications including differential diagnosis of primary site, grading, and increasingly expanding prognostic/therapeutic reasons.

For example, recently, IHC has been made available for evaluation of programmed death ligand 1 (PD-L1) in the tumor cells [30]. Programmed death (PD)-1 (CD279) is a co-inhibitory receptor present on the cell surface of monocytes, T lymphocytes, B lymphocytes, and natural killer cells [31]. It has 2 ligands: PD-L1 (B7-H1) and PD-L2 (B7-DC). Interaction between PD-1 and its ligands down-regulates the T-cell response by inhibiting T-cell receptor signaling. PD-L1 on tumor cells is upregulated. Studies revealed that barricading this interaction with antibodies to PD-1 or PD-L1 reverses this inhibition to regain anti-tumor T-cell activity with therapeutic benefits [31].

Discussing application of IHC in detail is beyond the scope of this chapter [28]. A few immunomarkers applicable to GI cancers are shown in Table 2.5 [16, 17, 30–32].

Molecular Pathology

The role of molecular tests in GI cancer is continuously increasing. Please refer to the chapter on this topic in this book for more details in addition to other publications on this topic [17, 33–35]. Here, it is important to understand some basic details related to these. The molecular tests may be DNA-based or RNA-based. Recently, the role of microRNA (miRNA) is evolving. DNA is very robust and miRNA is relatively stable. In contrast, RNA is quite unstable and requires special precautions and protocols due to ubiquity of RNAase (RNA-destroying enzyme) present in tissue samples and in the devices/steps at different stages of processing. However, currently, many refinements have been achieved in the application of RNA-based molecular tests performed on FFPE [36]. Thus, like IHC, most of the molecular tests could be performed on FFPE, which in general is the most easily available clinical material for performing elective molecular pathology test at any stage on the archived FFPE tissue. Also, it is important to know the proportion of viable tumor component in the FFPE section in comparison with background nontumor nucleated component. Many tests require a minimum fraction of tumor component for optimum results. One should check with the laboratory performing a particular molecular pathology test

Table 2.5 Application of immunomarkers in gastrointestinal cancers: a few examples

Diagnostic	
Evaluate invasion	
Cytokeratin (CK) (Pan cytokeratin)	Identify single cells in diffusely spreading carcinoma – especially in small biopsies
Differential for primary site	
CK 7 and CK 20 coordinate pattern	Broad scrutiny for primary site identification
BER/EP4	Adenocarcinoma metastases to serous fluid cavities
Organ/site/tumor-specific immunomarkers	
CDX2/ STAB 2/ CDH 17	Colorectal-intestinal, pancreato-biliary, upper GI
Arginase	Hepatocellular carcinoma
Albumin miRNA (CISH)	Hepatocellular carcinoma
Estrogen receptor	Breast, ovary
LCA	Lymphoproliferative lesions
PAX 8	Ovary, kidney
PSA/PAP	Prostrate
MART 1/melan A	Melanoma
Calretinin	Mesothelioma
CD117/PGDF/DOG1	Gastrointestinal stromal tumor (GIST)
TTF-1	Lung, thyroid
Organ/site-specific immunostaining pattern	
pCEA/CD10	Bile canalicular pattern in hepatocytes
CD34	Diffuse sinusoidal immunostaining pattern (hepatocellular carcinoma versus regenerating nodule)
CK 19	Identify small bile ducts in small biopsies in differential diagnosis of regenerating nodule versus hepatocellular carcinoma
Differentiation immunomarkers (with many exceptions)	
Synaptophysin, chromogranin, CD56, INSM1	Neuroendocrine differentiation
Cytokeratins	Broad epithelial differentiation
LCA	Broad hematopoietic differentiation
Vimentin	Broad sarcomatous differentiation
Prognostic	
MIB 1 (Ki 67) (especially dual color-Ki 67- nuclear Brown, with LCA-cytoplasmic-Red)	Grading of neuroendocrine tumors (NET), GIST, lymphoma [9a]
Mismatched repair (MMR) proteins – MLH1, PMS2, MSH2, MSH6 (loss of nuclear immunoreactivity to these immuomarkers)	Hereditary colon adenocarcinoma (Lynch syndrome) [17]
Therapeutic	
Her2/Neu	Gastric and gastroesophageal junction adenocarcinoma
PD-L1	Targeted antibodies [30–32]
CD117	GIST – tyrosine-kinase inhibitor [16]

regarding the minimum tumor proportion required for a specific test in their laboratory. This may be overcome by selectively dissecting out the tumor by various microdissection methodologies. For other molecular pathology tests, there may be specific protocols requiring fresh or frozen tissue or tissue collected in special medium/preservative such as RNAlater® [37]. All of these limitations should be taken into consideration prior to proceeding with any molecular tests on any specimen. The overview for approaching molecular pathology tests on GI cancer specimens is summarized in Fig. 2.4 [17, 30–32, 38–45].

Classification of Gastrointestinal Tumors

GI cancers have been classified traditionally at two levels: macroscopic and microscopic.

Macroscopic Classification

Ultimately, similar to other cancers, microscopic findings in GI cancers decide the final interpretation and classification. But, the macroscopic gross evaluation including tumor configuration, size, and anatomic site is an important step with extended practical application, especially during endoscopic examination. The tumors of tubular GIT may be classified based on the approach used for gastric tumors, which are generally divided into four types: type I (polypoid), type II (fungating), type III (ulcerated), and type IV (infiltrative, also called *linitis plastica*) [46]. Some macroscopic features of ulcerated lesions may help to distinguish a benign ulcer from an ulcerated carcinoma (type III). A small, punched-out, well-circumscribed ulcer with a smooth base and edematous regular margin favors a benign gastric ulcer. In comparison, an irregular ulcer with raised, firm borders with necrotic and hemorrhagic base, typically favors a malignant ulcer [47].

Similar to gastric cancer, colorectal cancer (CRC) can also be classified macroscopically [48]:

1. *Exophytic tumors*: usually large, polypoid lesions (typically in the cecum) are rarely obstructive.
2. *Infiltrative ulcerating tumors*: ulcer with irregular raised edges.
3. *Constricting annular tumors*: functionally obstructive lesion with firm consistency due to desmoplasia resulting in proximal dilatation with typical double-contrast "apple-core" sign.
4. *Diffuse tumors*: similar to linitis plastica of the stomach with infiltrative growth along the bowel wall.

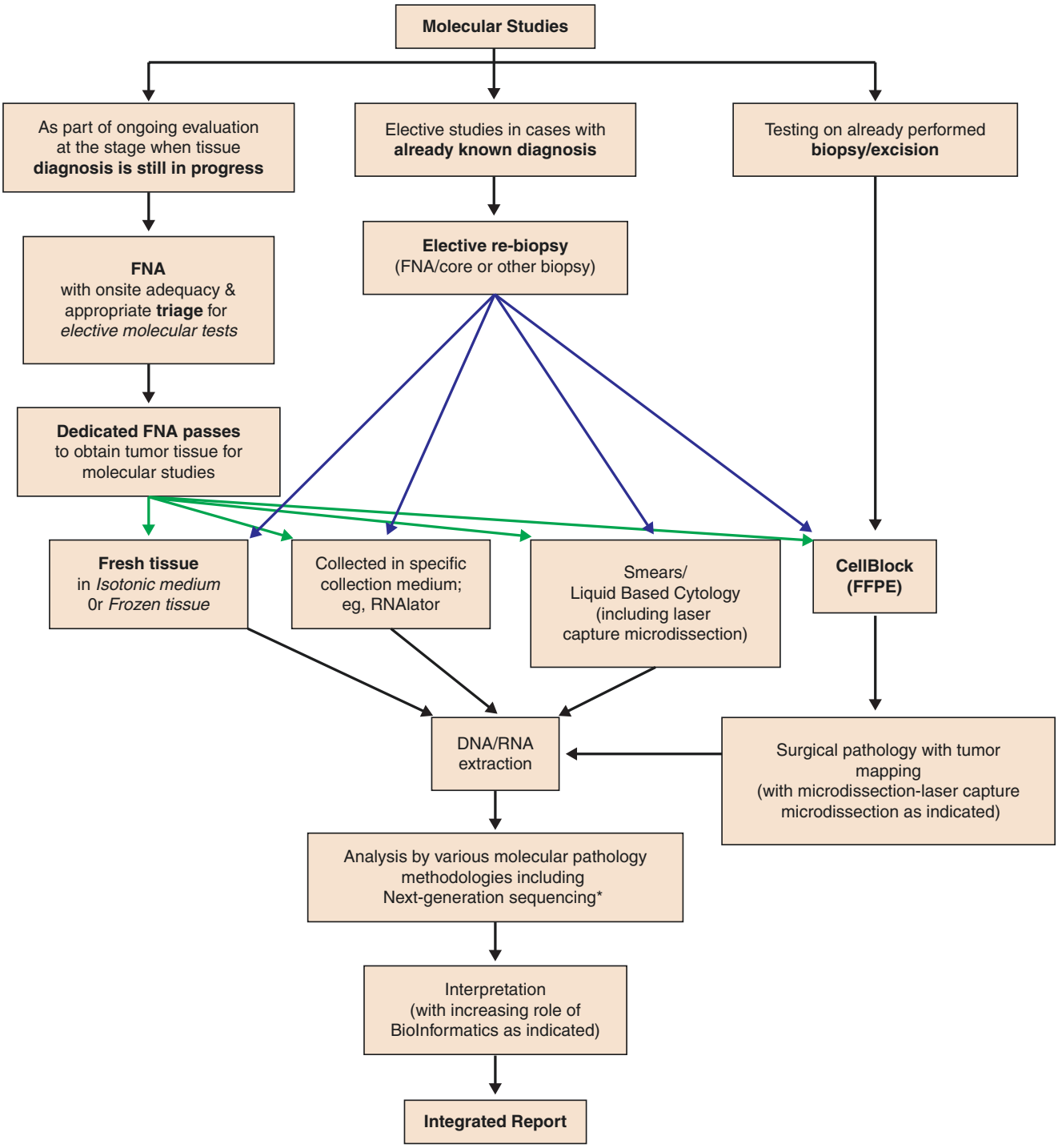


Fig. 2.4 Approach to evaluate commonly used molecular pathology tests and methodologies applicable to GI cancers (∗See references [17, 30–32, 38, 63–70])

Although macroscopic classification does not have a prognostic significance independent of the histological subtype [49], anatomic site does. *Right-sided t*umors – located in the cecum, ascending colon, hepatic flexure, or transverse colon – have a better prognosis as compared to left-sided tumors – located in the splenic flexure, descending colon, or sigmoid colon [50]. This may be related to tendency for microsatellite instability (MSI) in the right colon.

With the increasing role of endoscopy, macroscopic classification has evolved to categorize early neoplasia (type 0) of the digestive tract [51–53]. This classification distinguishes polypoid/protruded (type 0–I); nonpolypoid/nonprotruded, nonexcavated (type 0–II); and nonpolypoid, and excavated

(type 0–III) lesions. Type 0–II lesions are subdivided by the absence (type 0–IIa-elevated and type 0–IIb-flat) or presence (type 0–IIc) of a depression. This morphological macroscopic terminology applies to esophagus, stomach, and colon with increasing clinical relevance in the era of endoscopy [51]. But macroscopic features of GI cancers have limited diagnostic, predictive, and prognostic significance. Absolute dependence of staging on imaging findings without meticulous grossing of resection specimen is discouraged. Generally, malignant tumors are nonencapsulated with irregular infiltrative borders. They are usually large and solid with foci of necrosis/hemorrhages. As standard of practice, microscopic surgical pathology examination with tissue diagnosis is critical for appropriate management.

Microscopic Classification

CAP and other professional bodies have recommended internationally accepted terminology and diagnostic criteria established by the WHO for consistency and uniformity in pathological reporting (Table 2.6) [6, 54].

Table 2.6 Pathological classifications of various GI tumors (WHO 2000) [6]

Esophageal tumors
Epithelial tumors
Squamous cell papilloma 8052/0
Intraepithelial neoplasia
Squamous
Glandular (adenoma)
Carcinoma
Squamous cell carcinoma 8070/3
Verrucous (squamous) carcinoma 8051/3
Basaloid squamous cell carcinoma 8083/3
Spindle cell (squamous) carcinoma 8074/3
Adenocarcinoma 8140/3
Adenosquamous carcinoma 8560/3
Mucoepidermoid carcinoma 8430/3
Adenoid cystic carcinoma 8200/3
Small cell carcinoma 8041/3
Undifferentiated carcinoma 8020/3
Others
Carcinoid tumor 8240/3
Nonepithelial tumors
Leiomyoma 8890/0
Lipoma 8850/0
Granular cell tumor 9580/0
Gastrointestinal stromal tumor 8936/1
Benign 8936/0
Uncertain malignant potential 8936/1
Malignant 8936/3
Leiomyosarcoma 8890/3
Rhabdomyosarcoma 8900/3
Kaposi sarcoma 9140/3
Malignant melanoma 8720/3
Others – lymphoma
Secondary tumors
Melanoma

Table 2.6 (continued)

Gastric tumors
Epithelial tumors
Intraepithelial neoplasia – adenoma 8140/0
Carcinoma
Adenocarcinoma 8140/3
Intestinal type 8144/3
Diffuse type 8145/3
Papillary adenocarcinoma 8260/3
Tubular adenocarcinoma 8211/3
Mucinous adenocarcinoma 8480/3
Signet-ring cell carcinoma 8490/3
Adenosquamous carcinoma 8560/3
Squamous cell carcinoma 8070/3
Small cell carcinoma 8041/3
Undifferentiated carcinoma 8020/3
Others
Endocrine neoplasms of the stomach
1. Carcinoid – well-differentiated endocrine neoplasm
1.1 ECL-cell carcinoid
1.2 EC-cell, serotonin-producing carcinoid
1.3 G-cell, gastrin-producing tumor
1.4 Others
2. Small cell carcinoma – poorly differentiated endocrine neoplasm
3. Tumor-like lesions
Hyperplasia
Dysplasia
Nonepithelial tumors
Leiomyoma 8890/0
Schwannoma 9560/0
Granular cell tumor 9580/0
Glomus tumor 8711/0
Leiomyosarcoma 8890/3
GI stromal tumor 8936/1
Benign 8936/0
Uncertain malignant potential 8936/1
Malignant 8936/3
Kaposi sarcoma 9140/3
Others
Malignant lymphomas
Marginal zone B-cell lymphoma of MALT-type 9699/3
Mantle cell lymphoma 9673/3
Diffuse large B-cell lymphoma 9680/3
Others
Secondary tumors (breast, melanoma, etc.)

Table 2.6 (continued)

Small intestinal tumors
Epithelial tumors
Adenoma 8140/0
Tubular 8211/0
Villous 8261/0
Tubulovillous 8263/0
Intraepithelial neoplasia 2 (dysplasia) associated with chronic inflammatory diseases
Low-grade glandular intraepithelial neoplasia
High-grade glandular intraepithelial neoplasia
Carcinoma
Adenocarcinoma 8140/3
Mucinous adenocarcinoma 8480/3
Signet-ring cell carcinoma 8490/3
Small cell carcinoma 8041/3
Squamous cell carcinoma 8070/3
Adenosquamous carcinoma 8560/3
Medullary carcinoma 8510/3
Undifferentiated carcinoma 8020/3
Carcinoid (well-differentiated endocrine neoplasm) 8240/3
Gastrin cell tumor, functioning (gastrinoma) 8153/1 or nonfunctioning
Somatostatin cell tumor 8156/1
EC-cell, serotonin-producing neoplasm 8241/3
L-cell, glucagon-like peptide and PP/PYY-producing tumor
Mixed carcinoid–adenocarcinoma 8244/3
Gangliocytic paraganglioma 8683/0
Nonepithelial tumors
Lipoma 8850/0
Leiomyoma 8890/0
Gastrointestinal stromal tumor 8936/1
Leiomyosarcoma 8890/3
Angiosarcoma 9120/3
Kaposi sarcoma 9140/3
Others
Malignant lymphomas
Immunoproliferative small intestinal disease 9764/3 (includes α[alpha]-heavy-chain disease)
Western type B-cell lymphoma of MALT 9699/3
Mantle cell lymphoma 9673/3
Diffuse large B-cell lymphoma 9680/3
Burkitt lymphoma 9687/3
Burkitt-like/atypical Burkitt lymphoma 9687/3
T-cell lymphoma 9702/3
Enteropathy associated 9717/3
Unspecified 9702/3
Others
Secondary tumors
Polyps
Hyperplastic (metaplastic)
Peutz–Jeghers
Juvenile

Table 2.6 (continued)

Tumors of the appendix
Epithelial tumors
Adenoma 8140/02 (cystic counterpart – cystadenoma)
Tubular 8211/0
Villous 8261/0
Tubulovillous 8263/0
Serrated 8213/0
Carcinoma
Adenocarcinoma
8140/3 (cystic counterpart – cystadenocarcinoma)
Mucinous adenocarcinoma 8480/3
Signet-ring cell carcinoma 8490/3
Small cell carcinoma 8041/3
Undifferentiated carcinoma 8020/3
Carcinoid (well-differentiated endocrine neoplasm) 8240/3
EC-cell, serotonin-producing neoplasm 8241/3
L-cell, glucagon-like peptide
And PP/PYY-producing tumor
Others
Tubular carcinoid 8245/1
Goblet cell carcinoid (mucinous carcinoid) 8243/3
Mixed carcinoid–adenocarcinoma 8244/3
Nonepithelial tumors
Neuroma 9570/0
Lipoma 8850/0
Leiomyoma 8890/0
Gastrointestinal stromal tumor 8936/1
Leiomyosarcoma 8890/3
Kaposi sarcoma 9140/3
Others
Malignant lymphoma
Secondary tumors
Hyperplastic (metaplastic) polyp

(continued)

Table 2.6 (continued)

Tumors of the colon and rectum
Epithelial tumors
Adenoma 8140/0
Tubular 8211/0
Villous 8261/0
Tubulovillous 8263/0
Serrated 8213/0
Intraepithelial neoplasia 2 (dysplasia) associated with chronic inflammatory diseases
Low-grade glandular intraepithelial neoplasia
High-grade glandular intraepithelial neoplasia
Carcinoma
Adenocarcinoma 8140/3
Mucinous adenocarcinoma 8480/3
Signet-ring cell carcinoma 8490/3
Small cell carcinoma 8041/3
Squamous cell carcinoma 8070/3
Adenosquamous carcinoma 8560/3
Medullary carcinoma 8510/3
Undifferentiated carcinoma 8020/3
Carcinoid (well-differentiated endocrine neoplasm) 8240/3
EC-cell, serotonin-producing neoplasm 8241/3
L-cell, glucagon-like peptide and PP/PYY-producing tumor
Others
Mixed carcinoid–adenocarcinoma 8244/3
Others
Nonepithelial tumors
Lipoma 8850/0
Leiomyoma 8890/0
Gastrointestinal stromal tumor 8936/1
Leiomyosarcoma 8890/3
Angiosarcoma 9120/3
Kaposi sarcoma 9140/3
Malignant melanoma 8720/3
Others
Malignant lymphomas
Marginal zone B-cell lymphoma of MALT type 9699/3
Mantle cell lymphoma 9673/3
Diffuse large B-cell lymphoma 9680/3
Burkitt lymphoma 9687/3
Burkitt-like/atypical Burkitt lymphoma 9687/3
Others
Secondary tumors
Polyps
Hyperplastic (metaplastic)
Peutz–Jeghers
Juvenile

Tumors of the anal canal
Epithelial tumors
Intraepithelial neoplasia 1 (dysplasia)
Squamous or transitional epithelium
Glandular
Paget disease 8542/3
Carcinoma
Squamous cell carcinoma 8070/3
Adenocarcinoma 8140/3
Mucinous adenocarcinoma 8480/3
Small cell carcinoma 8041/3
Undifferentiated carcinoma 8020/3
Others
Carcinoid tumor 8240/3
Malignant melanoma 8720/3
Nonepithelial tumors
Secondary tumors

Table 2.6 (continued)

Tumors of the liver and intrahepatic bile ducts
Epithelial tumors
Benign
Hepatocellular adenoma (liver cell adenoma) 8170/01
Focal nodular hyperplasia
Intrahepatic bile duct adenoma 8160/0
Intrahepatic bile duct cystadenoma 8161/0
Biliary papillomatosis 8264/0
Malignant
Hepatocellular carcinoma (liver cell carcinoma) 8170/3
Intrahepatic cholangiocarcinoma 8160/3
(peripheral bile duct carcinoma)
Bile duct cystadenocarcinoma 8161/3
Combined hepatocellular and cholangiocarcinoma 8180/3
Hepatoblastoma 8970/3
Undifferentiated carcinoma 8020/3
Nonepithelial tumors
Benign
Angiomyolipoma 8860/0
Lymphangioma and lymphangiomatosis 9170/0
Hemangioma 9120/0
Infantile hemangioendothelioma 9130/0
Malignant
Epithelioid hemangioendothelioma 9133/1
Angiosarcoma 9120/3
Embryonal sarcoma (undifferentiated sarcoma) 8991/3
Rhabdomyosarcoma 8900/3
Others
Miscellaneous tumors
Solitary fibrous tumor 8815/0
Teratoma 9080/1
Yolk sac tumor (endodermal sinus tumor) 9071/3
Carcinosarcoma 8980/3
Kaposi sarcoma 9140/3
Rhabdoid tumor 8963/3
Others
Hematopoietic and lymphoid tumors
Secondary tumors
Epithelial abnormalities
Liver cell dysplasia (liver cell change)
Large cell type (large cell change)
Small cell type (small cell change)
Dysplastic nodules (adenomatous hyperplasia)
Low grade
High grade (atypical adenomatous hyperplasia)
Bile duct abnormalities
Hyperplasia (bile duct epithelium and peribiliary glands)
Dysplasia (bile duct epithelium and peribiliary glands)
Intraepithelial carcinoma (carcinoma in situ) 8500/211
Miscellaneous lesions
Mesenchymal hamartoma
Nodular transformation
(nodular regenerative hyperplasia)
Inflammatory pseudotumor

Table 2.6 (continued)

Tumors of the gallbladder and extrahepatic bile ducts
Epithelial tumors
Benign
Adenoma 8140/0
Tubular 8211/0
Papillary 8260/0
Tubulopapillary 8263/0
Biliary cystadenoma 8161/0
Papillomatosis (adenomatosis) 8264/0
Intraepithelial neoplasia (dysplasia and carcinoma in situ)
Malignant
Carcinoma
Adenocarcinoma 8140/3
Papillary adenocarcinoma 8260/3
Adenocarcinoma, intestinal type 8144/3
Adenocarcinoma, gastric foveolar type
Mucinous adenocarcinoma 8480/3
Clear cell adenocarcinoma 8310/3
Signet-ring cell carcinoma 8490/3
Adenosquamous carcinoma 8560/3
Squamous cell carcinoma 8070/3
Small cell carcinoma 8041/3
Large cell neuroendocrine carcinoma 8013/3
Undifferentiated carcinoma 8020/3
Biliary cystadenocarcinoma 8161/3
Carcinoid tumor 8240/3
Goblet cell carcinoid 8243/3
Tubular carcinoid 8245/1
Mixed carcinoid–adenocarcinoma 8244/3
Others
Nonepithelial tumors
Granular cell tumor 9580/0
Leiomyoma 8890/0
Leiomyosarcoma 8890/3
Rhabdomyosarcoma 8900/3
Kaposi sarcoma 9140/3
Others
Malignant lymphoma
Secondary tumors

Table 2.6 (continued)

Tumors of the exocrine pancreas
Epithelial tumors
Benign
Serous cystadenoma 8441/0
Mucinous cystadenoma 8470/0
Intraductal papillary-mucinous adenoma 8453/0
Mature teratoma 9080/0
Borderline (uncertain malignant potential)
Mucinous cystic neoplasm with moderate dysplasia 8470/1
Intraductal papillary-mucinous neoplasm with moderate dysplasia 8453/1
Solid-pseudopapillary neoplasm 8452/1
Malignant
Ductal adenocarcinoma 8500/3
Mucinous noncystic carcinoma 8480/3
Signet-ring cell carcinoma 8490/3
Adenosquamous carcinoma 8560/3
Undifferentiated (anaplastic) carcinoma 8020/3
Undifferentiated carcinoma with osteoclast-like giant cells 8035/3
Mixed ductal-endocrine carcinoma 8154/3
Serous cystadenocarcinoma 8441/3
Mucinous cystadenocarcinoma 8470/3
– Noninvasive 8470/2
– Invasive 8470/3
Intraductal papillary-mucinous carcinoma 8453/3
– Noninvasive 8453/2
– Invasive (papillary-mucinous carcinoma) 8453/3
Acinar cell carcinoma 8550/3
Acinar cell cystadenocarcinoma 8551/3
Mixed acinar-endocrine carcinoma 8154/3
Pancreatoblastoma 8971/3
Solid-pseudopapillary carcinoma 8452/3
Others
Nonepithelial tumors
Secondary tumors

Traditionally, tumor classification is based on type of tissue differentiation and is termed *histogenetic classification*, which categorizes different tumors with reference to various morphological features including: (1) site of primary tumor, (2) differentiation/histogenesis, (3) architectural phenotype, and (4) degree of differentiation (grade).

1. **Site of Primary Tumor:** Neoplasms of epithelium may be benign (*papillomas/adenomas*) or malignant (*carcinomas*). Similarly, those of connective tissue may be benign (various *–omas*) or malignant (*sarcomas*). Although generally there is good concordance between the type of normal tissue and type of neoplasm, some tumors with discordant differentiation may be seen in odd tissues. For example, carcinomas with total (as squamous cell carcinoma) or partial (adenosquamous carcinoma) squamous differentiation may be seen in organs such as the colon, rectum, and pancreas, which normally do not have squamous epithelium.
2. **Differentiation/Histogenesis:** Carcinomas demonstrating glandular growth pattern are *adenocarcinomas* versus *squamous cell carcinomas* with squamous differentiation.

Other than in the esophagus and anus (which in a significant proportion in these sites are *squamous cell carcinoma*), most of the GI carcinomas are *adenocarcinomas*.

Adenocarcinomas may be subdivided morphologically into various subtypes such as *usual type* (with glands of variable size, shapes, and maturity in the background of variable proportion of desmoplastic stroma); *mucinous type* (adenocarcinomas comprising of more than 50% component producing abundant secretory mucin (the term "adenocarcinoma with mucinous differentiation" may be used for tumors with marginal proportion of mucinous component >10% but <50%); *signet-ring cell type* (adenocarcinomas showing at least 50% signet-ring cells with cytoplasmic mucin vacuole pushing the nucleus).

Benign/malignant neoplasms of connective tissue, adipose tissue, smooth muscle, skeletal muscle, vessels, cartilage, and bone are broadly labeled respectively as fibroma/fibrosarcoma, lipoma/liposarcoma; leiomyoma/leiomyosarcoma; rhabdomyoma/rhabdomyosarcoma, angioma/angiosarcoma; chondroma/chondrosarcoma; and osteoma/osteosarcoma.

The tumors of hematopoietic and lymphoid tissues are *leukemias* and *lymphomas*. In the adult population, the majority of malignant neoplasms of tubular GIT are *carcinomas* followed by lymphomas and sarcomas, which are relatively the predominant tumor in the pediatric population.

3. **Architectural Phenotype:** Like other tumors, GI tumors may be classified based on growth pattern and microscopic architecture, which also provides important histogenetic clues while interpreting the tumor biopsies or resection specimens. Architectural pattern of epithelial tumors may be *tubular* (branching tubules of variable sizes); *papillary* (finger-like projections with fibrovascular central cores); *solid* or *trabecular* (seen in medullary carcinoma of the colon, neuroendocrine tumors, and hepatocellular carcinoma). Some tumors may show a *cystic* pattern (seen in the pancreas but relatively uncommon in tubular GI tumors, as mucinous carcinomas and endothelial tumors such as lymphangioma or hemangioma). Even solid tumors including stromal tumors/sarcomas, lymphomas, and carcinomas with central necrosis may present as cystic lesions, especially at imaging level. However, in general, growth pattern of GI tumors has little prognostic significance [55, 56]. Recently, a polyp with serrated glandular architecture has been linked as a precursor lesion for colorectal carcinomas [57].

A few examples suggesting applications of growth patterns for tumor classifications include *Lauren classification*, categorizing gastric cancers into different types: *Intestinal, diffuse*, mixed, and *indeterminate/unclassified* [58], in which diffuse growth pattern with highly unfavorable prognosis has macroscopic linitis plastica appearance with signet-ring cells at the microscopic level [59]. Colon cancers with *tumor budding* in the form of single cells or groups of less than 4 tumor cells at the invasive margin have worse prognosis and are associated with a diffuse growth pattern [60–65].

4. **Degree of Differentiation (Grade):** Tumor grade reflects the biological properties of the tumor. In general high-grade tumors are associated with aggressive biological behavior. The clinical significance of grading may be different for each tumor category. As an example, carcinomas or sarcomas with lower grade may be biologically less aggressive and amenable to surgical excision as compared to higher grade counterparts. On the other hand, low-grade lymphomas, although more indolent and slow growing than high-grade lymphomas, are difficult to be cured by medical therapy.

Although there are various approaches in grading tumors, the most commonly applied is the degree of resemblance of the tumor morphology to its non-neoplastic counterpart. Several microscopic features are taken into consideration for grading a tumor, including the anatomic site of origin of the tumor, the class of the tumor (i.e., carcinoma, sarcoma, or lymphoma), and the histological subtype within the class. The simplest approach applied for grading includes degree of gland formation in adenocarcinomas versus degree of keratinization in squamous cell carcinomas [56]. Most grading systems assign the grade based on the most poorly differentiated area. Some consider average of grades in different areas of the tumor. Arbitrarily most pathologists grade GI cancers into 4 grades: *Well differentiated* (grade 1), *moderately differentiated* (grade 2), *poorly differentiated* (grade 3), and *undifferentiated* (grade 4). Due to this subjective judgment left to the individual observer, there may not be reproducible outcome with significant degree of interobserver variability [66]. Despite these limitations, grading has some prognostic significance in most gastrointestinal malignancies [55, 56]. In addition, if the grade of the primary tumor is known, it may help while evaluating the interpretation of metastases at later stage during comparative review.

The CAP-suggested grading system is based on a semiquantitative approach for improved reproducibility and considers the proportion of neoplastic glands in the tumor: *grade X* (grade cannot be assessed); *grade 1* (well differentiated) – more than 95% glands; *grade 2* (moderately differentiated) – 50–95% glands; *grade 3* (poorly differentiated) – 5–49% glands; and *grade 4* (undifferentiated) – fewer than 5% glands [56]. Further simplification of this grading system has suggested a 2-tiered system for improved reproducibility [49]. *Higher grade tumors* demonstrate adverse prognosis independent of the stage. However, some poorly differentiated colorectal adenocarci-

nomas, such as those with MSI, may have better prognoses [67]. This simple approach has to be modified for some subtypes of carcinoma (e.g., medullary carcinoma of the colon is left ungraded; signet-ring carcinoma is defined as poorly differentiated or high-grade).

Other tumors including neuroendocrine tumors, sarcomas, and lymphomas have a special grading system based on different parameters such as proliferation index (mitotic figures or Ki-67 index estimation), necrosis, and other features.

Staging of Malignant Gastrointestinal Tumors

Staging is one of the best but simplest time-tested approaches for stratifying malignant neoplasms for prognostic grouping and is very important for planning the therapeutic management of the case. A staging system based on TNM classification standardized by the AJCC and UICC is recommended by CAP [12, 13, 15]. It has been used all over North America by national, regional, and local tumor registries and is also accepted internationally.

General Principles of the TNM Staging

TNM staging is based on classification and grouping of: "T" for the primary tumor status, "N" for regional lymph node status, and "M" for distant metastatic disease status (Table 2.7) [15, 68]. Final AJCC stage is assigned progressively from stage I through stage IV based on various combinations of staging in each category standardized for the individual organ system (see TNM staging of colon cancer as example in Table 2.1, Fig. 2.5) [15]. Lymphoma has a special staging system without applying the TNM approach for most lymphomas, except some types such as primary cutaneous lymphoma [15]. Although in general AJCC staging criteria are practiced, some ongoing approaches continue to evolve and claim better prognostic correlation [69].

More features are added to include other details: prefix "p" refers to the *pathological* classification; prefix "c" for the *clinical* classification. Prefix "r" is used for *recurrent tumors* following curative therapy (subject to the documentation of disease free interval) (Table 2.8) [12, 13, 15].

"R" classification is for *residual tumor* after primary therapy (e.g., curative surgical resection):

Table 2.7 TNM staging: general guidelines [15]

Topic	Rules
Microscopic confirmation	Microscopic confirmation is necessary for TNM classification, including clinical classification (with rare exception)
	In rare clinical scenarios, patients who do not have any biopsy or cytology of the tumor may be staged. This is recommended in rare clinical situations, only if cancer diagnosis is NOT in doubt. In the absence of histological confirmation, survival analysis may be performed separately from staged cohorts with histological confirmation. Separate survival analysis is not required if clinical findings support a cancer diagnosis and specific site
	Example: Lung cancer diagnoses by CT scan only, that is, without a confirmation biopsy[a]
Time frame/staging window for determining clinical stage	Information gathered about the extent of the cancer is part of clinical classification: From date of diagnosis before initiation of primary treatment or decision for watchful waiting or supportive care to one of the following time points, whichever is shortest: 4 months after diagnosis To the date of cancer progression if the cancer progresses before the end of the 4-month window; data on the extent of the cancer are only included before the date of observed progression
Time frame/staging window for determining pathological stage	Information including clinical staging data and information from surgical resection and examination of the resected specimens – if surgery is performed before the initiation of radiation and/or systemic therapy – from the date of diagnosis: Within 4 months after diagnosis To the date of cancer progression if the cancer progresses before the end of the 4-month window; data on the extent of the cancer are included only before the date of observed progression And includes any information obtained about the extent of cancer up through completion of definitive surgery as part of primary treatment if that surgery occurs later than 4 months after diagnosis and the cancer has not clearly progressed during the time window *Note*: Patients who receive radiation and/or systemic therapy (neoadjuvant therapy) before surgical resection are not assigned a pathological category or stage, and instead, they are staged according to post-neoadjuvant therapy criteria
Time frame/staging window for staging post-neoadjuvant therapy or post-therapy	After completion of neoadjuvant therapy, patients should be staged as follows: yc: post-therapy clinical yp: post-therapy pathological The time frame should be such that the post-neoadjuvant surgery and staging occur within a time frame that accommodates disease-specific circumstances, as outlined in the specific chapters and in relevant guidelines *Note*: Clinical stage should be assigned before the start of neoadjuvant therapy

(continued)

Table 2.7 (continued)

Topic	Rules
Progression of disease	If there is documented progression of cancer before therapy or surgery, only information obtained before the documented progression is used for clinical and pathological staging Progression does not include growth during the time needed for the diagnostic workup, but rather a major change in clinical status Determination of progression is based on managing physician judgment and may result in a major change in the treatment plan
Uncertainty among T, N, or M categories, and/or stage groups: rules for clinical decision making	If uncertainty exists regarding how to assign a category, subcategory, or stage group, the lower of the **two possible** categories, subcategories, or groups is assigned for T, N, or M Prognostic stage group/stage group Stage groups are for patient care and prognosis based on data. Physicians may need to make treatment decisions if staging information is uncertain or unclear *Note*: Unknown or missing information for T, N, M, or stage group is never assigned the lower category, subcategory, or group
Uncertainty rules do not apply to cancer registry data	If information is not available to the cancer registrar for documentation of a subcategory, the main (umbrella) category should be assigned (e.g., T1 for a breast cancer described as <2 cm in place of T1a, T1b, or T1c) If the specific information to assign the stage group is not available to the cancer registrar (including subcategories or missing prognostic factor categories), the stage group should not be assigned but should be documented as unknown
Prognostic factor category information is unavailable	If a required prognostic factor category is unavailable, the category used to assign the stage group is: X If the prognostic factor is unavailable, default to assigning the anatomic stage using clinical judgment
Grade	The recommended histological grading system for each disease site and/or cancer type, if applicable, is specified in each chapter and should be used by the pathologist to assign grade The cancer registrar will document grade for a specific site according to the coding structure in the relevant disease site chapter
Synchronous primary tumors in a single organ: (*m*) suffix	If multiple tumors of the same histology are present in one organ: The tumor with the highest T category is classified and staged The (*m*) suffix is used An example of a preferred designation is: pT3(m) N0 M0 If the number of synchronous tumors is important, an acceptable alternative designation is to specify the number of tumors. For example, pT3(4) N0 M0 indicates four synchronous primary tumors *Note*: The (*m*) suffix applies to multiple invasive cancers. It is not applicable for multiple foci of in situ cancer or for a mixed invasive and in situ cancer
Synchronous primary tumors in paired organs	Cancers occurring at the same time in each of paired organs are staged as separate cancers. Examples include breast, lung, and kidney **Exception**: For tumors of the thyroid, liver, and ovary, multiplicity is a T-category criterion, and thus, multiple synchronous tumors are not staged independently
Metachronous primary tumors	Second or subsequent primary cancers occurring in the same organ or in different organs outside the staging window are staged independently and are known as metachronous primary tumors Such cancers are not staged using the y prefix
Unknown primary or no evidence of primary tumor	If there is no evidence of a primary tumor, or the site of the primary tumor is unknown, staging may be based on the clinical suspicion of the organ site of the primary tumor, with the tumor categorized as T0. The rules for staging cancers categorized as T0 are specified in the relevant disease site chapters **Example**: An axillary lymph node with an adenocarcinoma in a woman, suspected clinically to be from the breast, may be categorized as T0 N1 (or N2 or N3) M0 and assigned Stage II (or Stage III) **Examples of exception**: The T0 category is not used for head and neck squamous cancer sites, as such patients with an involved lymph node are staged as unknown primary cancers using the "Cervical Nodes and Unknown Primary Tumors of the Head and Neck" system (T0 remains a valid category for human papillomavirus [HPV]-associated and Epstein–Barr virus [EBV]-associated oropharyngeal and nasopharyngeal cancers)
Date of diagnosis	It is important to document the date of diagnosis, because this information is used for survival calculations and time periods for staging The date of diagnosis is the date a physician determines the patient has cancer. It may be the date of a diagnostic biopsy or other microscopic confirmation or of clear evidence on imaging. This rule varies by disease site and shares similarities with the earlier discussion on microscopic confirmation

Original and primary source for this information is the *AJCC Cancer Staging Manual, Eighth Edition* (2017) published by Springer International Publishing

[a]Author's note: Recommend pathology reporting using CAP cancer protocols [68]

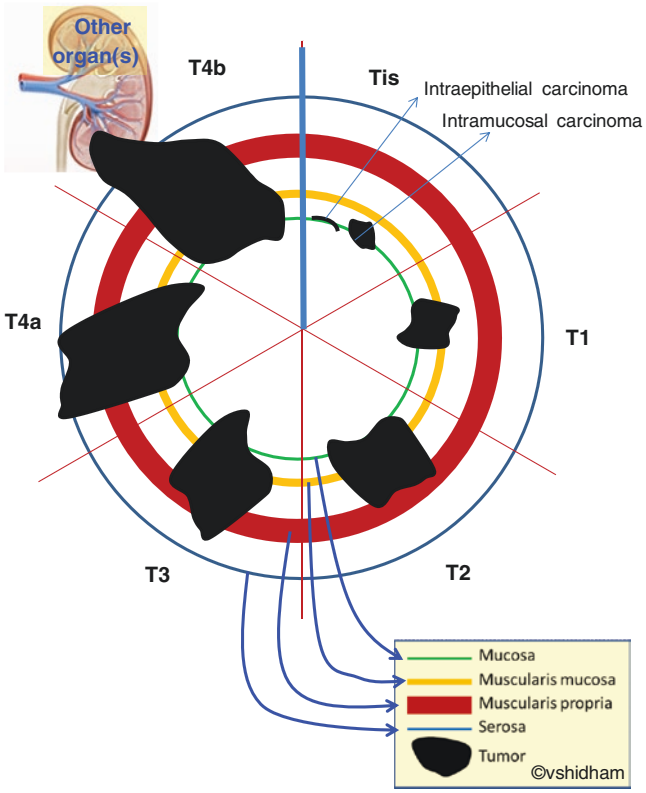


Fig. 2.5 T staging of colon carcinoma as example (see Table 2.1) [13]

- **R0** – *negative* for residual disease after definitive therapy (after curative surgical resection or total remission without detectable residual tumor)
- **R1**– residual tumor with *microscopically positive* resection margin
- **R2** – residual tumor with *macroscopically positive* resection margin

R classification is not usually followed by most institutions; instead, the report includes information on *resection margins*.

T Category

T staging (Table 2.9) for tubular GI cancer is assigned based on the depth of invasion of the primary tumor into various layers with incremental status as it invades from superficial to deeper layers (Tables 2.1 and 2.2, Fig. 2.5) [15]. For some tumors, for example liver tumors, it is based on other features such as size, vascular invasion, and multifocality.

Carcinoma in situ (pTis) includes *intraepithelial carcinoma* (when malignant cells are still restricted superficial to the basement membrane and have not invaded beyond it) and *intramucosal carcinoma* (in which tumor cells invade lamina propria without invading muscularis mucosa into submucosa). However, use of these terminologies may be confusing if applied randomly. In the colon, both *intraepithelial*

Table 2.8 Staging classifications/designator rules [15]

Classification	Designation	Details
Clinical	cTNM or TNM	Criteria: used for all patients with cancer identified before treatment It is composed of diagnostic workup information, until first treatment, including: Clinical history and symptoms Physical examination Imaging Endoscopy Biopsy of the primary site Biopsy or excision of a single regional node or sentinel nodes, or sampling or regional nodes, with clinical T Surgical exploration without resection Other relevant examinations *Note*: Exceptions exist by site, such as complete excision of primary tumor for melanoma
Pathological	pTNM	Criteria: used for patients if surgery is the first definitive therapy It is composed of information from: Diagnostic workup from clinical staging combined with Operative findings Pathology review of resected surgical specimens
Post-therapy or post-neoadjuvant therapy	ycTNM or ypTNM	For purposes of post-therapy or post-neoadjuvant therapy, *neoadjuvant therapy* is defined as systemic and/or radiation therapy given before surgery; primary radiation and/or systemic therapy is treatment given as definitive therapy without surgery
		yc The yc classification is used for staging after primary systemic and/or radiation therapy, or after neoadjuvant therapy and before planned surgery **Criteria**: First therapy is systemic and/or radiation therapy
		yp The yp classification is used for staging after neoadjuvant therapy and planned post-neoadjuvant therapy surgery **Criteria**: First therapy is systemic and/or radiation therapy and is followed by surgery.

(continued)

Table 2.8 (continued)

Classification	Designation	Details
Recurrence or retreatment	rTNM	This classification is used for assigning stage at time of recurrence or progression until treatment is initiated. **Criteria**: Disease recurrence after disease-free interval or upon disease progression if further treatment is planned for a cancer that Recurs after a disease-free interval Progresses (without a disease-free interval)
		rc Clinical recurrence staging is assigned as rc
		rp Pathological staging information is assigned as rp for the rTNM staging classification. This classification is recorded in addition to and does not replace the original previously assigned clinical (c), pathological (p), and/or post-therapy (yc, yp) stage classifications, and these previously documented classifications are not changed
Autopsy	aTNM	This classification is used for cancers not previously recognized that are found as an incidental finding at autopsy and not suspected before death (i.e., this classification does not apply if an autopsy is performed in a patient with a previously diagnosed cancer) **Criteria**: No cancer suspected prior to death Both clinical and pathological staging information is used to assign a TNM

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual, Eighth Edition* (2017) published by Springer International Publishing

Table 2.9 Summary of TNM classification rules based on the *AJCC Cancer Staging Manual, Eighth Edition* (2017) [15]

T stage	N stage	M stage
Determined by *site-specific features* based on *size* and/or local *extension*	Determined by disease-specific rules based on number and location of *positive regional nodes*	Determined by positive biopsy of the metastatic site (pM1)
cT: *Clinical assessment* of T based on physical examination, imaging endoscopy, and biopsy and surgical exploration *without resection*	Minimum number of lymph nodes to be examined for staging defined by site and disease type However, N staging is performed based on pathological evaluation of sampled nodes even if minimum number could not be sampled	cM – clinical M classification is based only on history and examination Imaging of distant organ sites NOT required to assign cM0
pT: Pathological assessment of T based on microscopic evaluation of the resected tumor (or biopsy only if it assigns the highest T stage)	Pathological assessment of the primary tumor (pT) is must to assign pathological assessment of nodes (pN) except with unknown primary (T0)	pM0 – pathological M0 is NOT a valid category and may not be assigned. If a biopsy of suspected metastatic site is negative, it should be staged as cM0
pT generally based on single resection. If resected as >1 specimen, reasonable estimation is required to assess combined size/extension Disease-specific rules may apply	Pathological status of lymph node or sentinel node(s) without pT but with only clinical T (cT) is classified as clinical nodal status (cN)	Case with pathological T and N may be grouped as pathological TNM using clinical M designator (cM0 or cM1) (e.g., pT1 pN0 cM0 = pathological stage I)
Tumor size recorded in *whole millimeters* (smaller fractions are rounded to the nearest whole millimeter: 1 through 4 rounded down, and 5 through 9 rounded up)	Pathological status of a single node or nodes in the highest N category is classified as pN even in the absence of pathological information on other nodes	Case with pathological M1 (pM1) may be grouped as clinical and pathological Stage IV regardless of "c" or "p" status of T and N (e.g., cT1 cN1 pM1 = clinical or pathological stage IV)
Case may be classified by pT or pN without resection if microscopically *confirmed by biopsy*	*Sentinel lymph node* biopsy is denoted with (sn), e.g., pN0(sn), pN1(sn)	ITC in metastatic sites (e.g., bone marrow), circulating tumor cells (CTC), or disseminated tumor cells (DTC) classified as cM0(i+)
	Lymph nodes with only *isolated tumor cells* (ITC) are staged as pN0 (disease-specific rules apply, e.g., melanoma) Standard definition of ITC is cluster of tumor cells smaller than 0.2 mm in greatest dimension. These are usually not detected by HE but by special technique such as IHC	Serous effusion fluids positive for malignant cells is equivalent to distant metastasis
	Direct extension of primary tumor into regional node is classified as node positive and is part of pN	"MX" is eliminated in AJCC (2010) seventh edition
	Tumor nodule with smooth contour in regional node area classified as positive node	
	When size is the criterion for N category, stage *by size of metastasis*, **not size of node** when reported (unless specified in disease-specific in disease-specific rules)	

For more detailed updated rules, refer to *AJCC Cancer Staging Manual, Eighth Edition* (2017) published by Springer International Publishing. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois

carcinoma and *intramucosal carcinoma* are equivalent and have been used interchangeably.

Tumor invading an adjacent organ in contiguity (e.g., colonic carcinoma invading liver or even other segment of tubular GIT) is part of T staging and is not distant metastasis [15]. Similarly, sideways horizontal spread of tumor to the adjacent segment of tubular GIT (e.g., cecal carcinoma spreading along the lumen to adjacent ascending colon and/or adjacent terminal ileum) is also part of pT staging and not distant metastasis [15]. On the other hand, penetration of tumor through a lymph node capsule into a regional lymph node is considered nodal metastasis for N staging.

For multiple primary tumors of tubular GIT, T stage is assigned as per the highest category. However, multiplicity of tumor assigns it a specific T stage in the liver [15].

T staging for some special tumors such as GIST and NET have a special approach. It is based on the size of the tumor in GIST [15] and on the extent of invasion with tumor size in NET (Table 2.2) [15].

N Category

N staging is assigned based on status of regional lymph nodes evaluated conventionally by examining HE-stained sections (Table 2.9) [15]. If lymph nodes are grossly positive, only a representative section is submitted for confirmation. However, grossly negative or equivocal lymph nodes are submitted entirely [49]. The number of lymph nodes that could be evaluated from any resection specimen depends on a variety of factors including anatomic nature of specimen, the length of the resected segment, type of surgical procedure, chemo/radiation therapy status prior to resection, and/or technical skill/diligence on the part of the dissector grossing the specimen. The number of lymph nodes sampled from a node-negative colorectal cancer specimen has been suggested to be at least 12 lymph nodes [70, 71]. At least 1 positive or negative lymph node is needed for assigning pathological N (pN) staging.

Discontinuous spread or *tumor deposits* (TD) in subserosa, mesentery, and nonperitonealized pericolic or perirectal tissues, although not nodal metastases, are considered under N category. These should be distinguished from totally replaced lymph nodes (which are counted as lymph nodes) or venous invasion with extravascular spread (considered as V1/V2).

Positivity of nonregional lymph nodes for tumor is considered distant metastasis and is not part of pN staging, but belongs to pM staging [12, 13, 15].

M Category

Metastasis to any distant organ or tissue including any nonregional lymph node is considered for M staging (Table 2.9) [15]. Presence of isolated tumor cells in the bone marrow, peritoneal seeding, and positive serous fluid cytology are also considered metastases [15].

Satellite lesions (skip lesions) present as multiple tumor foci in adjacent bowel along the mucosa or submucosa are not distant metastases [15]. These must be distinguished from synchronous primary tumors.

Additional Features

There are a few additional features (Table 2.8 [15]) that should be communicated in the final surgical pathology report of excised GI cancer specimens (Table 2.10) [10, 12, 13, 15, 49, 55, 56, 60–65, 72]. Although these features are not reported specifically as an individual category, currently they are a routine part of the CAP cancer protocol in the final pathology report (see colon cancer CAP protocol as example in Table 2.11) [10].

Table 2.10 Additional features to be communicated in final surgical pathology report of excision specimens [10]

Feature	Remarks
L category (*lymphatic invasion by tumor*) [12, 15]	Lymphatic invasion is considered adverse prognostic factor in almost all gastrointestinal carcinomas [49, 55, 56, 72]. *L0: Lack of lymphatic invasion* *L1: Positive for lymphatic invasion*
V category (*venous invasion by tumor*) [12, 15]	Invasion by malignant cells into the large vessels within the tumor mass (*intramural venous invasion*) or in the adjacent vessel visible even on gross or on imaging (*extramural venous invasion*) is independent adverse prognostic factor for many GI cancers, especially gastric carcinomas, pancreatic carcinomas, colorectal carcinomas, hepatocellular carcinomas, and gastrointestinal sarcomas [55]. *V0: Lack of venous invasion* *V1: Microscopic venous invasion* *V2: Macroscopic venous invasion* CAP recommendation: Submit *at least 3 tissue blocks (preferably, 5 blocks)* from the deepest portion of the tumor [37]. Some studies recommend routine *elastic stain* for venous invasion detection [73].
PN category (*perineural invasion*)	Perineural invasion has also been regarded stage-independent adverse prognostic factor especially in some GI cancers such as pancreas and colon [72]. However, studies supporting this unequivocally are quantitatively and qualitatively limited.
Morphology of tumor periphery	Pattern of growth along the periphery of the tumor has been reported to be independent prognostic feature [49, 55, 56, 74]. Colonic adenocarcinoma variant such as *medullary carcinoma* with pushing borders usually has a favorable prognosis even though it has higher grade histomorphology [10]. *Tumor budding* associated with poor prognosis in colon adenocarcinoma is defined as isolated single cells or tiny groups of tumor cells (up to four) invading the stroma [60–65].

Although not reported specifically as individual category, currently these features are routine part of CAP cancer protocol in the final pathology report

Table 2.11 Recommended reporting protocol of various resections of cancers[a] using colon/rectal cancer as an example standardized by the College of American Pathologists (CAP) [10]

Colon and rectum ***(resection, including transanal disk excision of rectal neoplasms)***
Specimen:
Procedure:
+ Specimen length
Tumor site
+ Tumor location
Above or below peritoneal reflection
Tumor size
Greatest dimension: ___ cm
+ Additional dimensions: ___ × ___ cm
Macroscopic tumor perforation
+ Macroscopic intactness of mesorectum
Histological type
Histological grade
+ Histological features suggestive of microsatellite instability
+ Intratumoral lymphocytic response (tumor-infiltrating lymphocytes)
+ Peritumor lymphocytic response (Crohn-like response)
+ Tumor subtype and differentiation (select all that apply)
+ Mucinous tumor component (specify percentage)
+ Medullary tumor component
+ High histological grade (poorly differentiated)
Microscopic tumor extension
Margins
Proximal margin
Distal margin
Circumferential (radial) or mesenteric margin
Mucosal margin (noncircumferential transanal disk excision) (required only if applicable)
Other margin(s) (required only if applicable): Specify margin(s)
Treatment effect (applicable to carcinomas treated with neoadjuvant therapy)
Lymph-vascular invasion
Perineural invasion
Tumor deposits (discontinuous extramural extension)
+ Type of polyp in which invasive carcinoma arose
Pathological staging (pTNM)
TNM descriptors (required only if applicable) (select all that apply)
m (multiple primary tumors)
r (recurrent)
y (post-treatment)
Primary tumor (pT)
Regional lymph nodes (pN)
Number of lymph nodes examined
Number of lymph nodes involved
Distant metastasis (pM)
+ Additional pathological findings
+ Ancillary studies (please see *the CAP Colorectal Biomarker Template)*
If any biomarker is under testing and pending, it should be mentioned under the comments.
+ Comment(s)
+ This information is *optional* because it may be clinically important but is not yet validated and may not be of practical application for regular application in patient management.

[a]All templates are available at CAP website site [10] and show detailed options to be selected along with detailed instructions under various notes

Conclusion

Morphological evaluation with ancillary tests such as immunophenotyping and histochemistry is, and will continue to be, the most critical pivotal component in the management of GI cancers. The current advances in molecular pathology have increased its role and have become an integral part of management in addition to conventional AJCC staging [10].

In future, increasing insight into the molecular biology of all GI cancers including overexpression and/or repression of various genes as well as epigenetic changes would establish a better understanding with ongoing advances in achieving improved tumor classification, diagnosis, prognosis, and targeted personalized therapies [17, 33–35]. Generally, both conventional pathological examination and new molecular tests are required for proper evaluation of any GI cancer for diagnostic and therapeutic decisions. Application of any new biomarkers cannot be justified until the findings demonstrate a convincing positive impact on clinical management. The ongoing advances would improve the understanding in molecular biology of various GI cancers and develop treatment algorithms with targeted therapies tailored for individual patient care as personalized medicine evolves [75].

Acknowledgments The author thanks Paul Tranchida, MD (Cytopath); Hayan Jaratli, MD (Hempath and GI path); Fazlul Sarkar, PhD (Molecular path); and Deepti Munjal, MD (Hem-Onc) for their critical input. Scientific draft editing for improving this chapter by Elly Landolfi, MD (Cytopathology fellow); Anjani Shidham, BS; and Andrea Black, CT (ASCP)^{CM} is greatly appreciated. I also thank Kathy Rost; Yilan Li, MD, PhD (Cytopathology fellow); and Olubunmi Shoyele, MD (Cytopathology fellow) for diligent copy-editing of the page proofs of the final chapter.

References

1. Paull PE, Hyatt BJ, Wassef W, Fischer AH. Confocal laser endomicroscopy: a primer for pathologists. Arch Pathol Lab Med. 2011;135:1343–8.
2. Liu JTC, Loewke NO, Mandella MJ, Levenson RM, Crawford JM, Contag CH. Point-of-care pathology with miniature microscopes. Anal Cell Pathol. 2011;34(3):81–98.

3. Jabbour JM, Saldua MA, Bixler JN, Maitland KC. Confocal endomicroscopy: instrumentation and medical applications. Ann Biomed Eng. 2012;40(2):378–97.
4. Newton RC, Kemp SV, Shah PL, Elson D, Darzi A, Shibuya K, Mulgrew S, Yang GZ. Progress toward optical biopsy: bringing the microscope to the patient. Lung. 2011;189(2):111–9.
5. Carignan CS, Yagi Y. Optical endomicroscopy and the road to real-time, in vivo pathology: present and future. Diagn Pathol. 2012;7:98. Review.
6. Hamilton SR, Aaltonen LA, editors. Pathology and genetics of tumours of the digestive system. World Health Organization Classification of Tumours. International Agency for Research on Cancer (IARC). Lyon: IARC Press; 2000.
7. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39(6):707–12.
8. Zhao WY, Xu J, Wang M, Zhang ZZ, Tu L, Wang CJ, et al. Prognostic value of Ki67 index in gastrointestinal stromal tumors. Int J Clin Exp Pathol. 2014;7(5):2298–304.
9. Memorial Sloan Kettering Cancer Center. Gastrointestinal stromal tumor nomogram. https://www.mskcc.org/nomograms/gastrointestinal/stromal-tumor.

9a. Mejias-Badillo L, Bhalla A, Salem N, Thomas S, Shidham V. Evaluation of Ki-67 (MIB-1) labeling index with dual-color immunocytochemistry (Ki-67 with LCA) for grading of pancreatic neuroendocrine tumors. Lab Invest. 2015;95(Supplement1):129A (Abstract 501).

10. CAP Cancer Protocol. http://www.cap.org/web/home/resources/cancer-reporting-tools/cancer-protocol-templates?_afrLoop=464502758350895#%40%3F_afrLoop%3D464502758350895%26_adf.ctrl-state%3Daixxnr9k6_4.
11. American Join Committee on Cancer (AJCC). AJCC cancer staging manual. 6th ed. New York: Springer; 2002.
12. Wittekind C, Hutter R, Greene FL, Klimpfinger M, Sobin LH, International Union Against Cancer. TNM Atlas: illustrated guide to the TNM classification of malignant tumors. 5th ed. New York: Wiley·Liss; 2005.
13. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
14. Karpeh MS Jr, Brennan MF. Gastric carcinoma. Ann Surg Oncol. 1998;5:650–6.
15. Amin MB, editor. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
16. Demetri GD. Differential properties of current tyrosinee kinase inhibitors in gastrointestinal stromal tumors. Semin Oncol. 2011;38(Suppl 1):S10–9.
17. Bhalla A, Zulfiqar M, Weindel M, Shidham VB. Molecular diagnostics in colorectal carcinoma. Clin Lab Med. 2013;33(4):835–59.
18. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors. A review of nomenclature, grading, and staging systems. Pancreas. 2010;39:707–12.
19. Shidham VB. Overview of FNA procedure: strength, weakness, and training. http://www.slideshare.net/vshidham/overview-of-fna-procedure-s-k-navale-medical-college-pune-india.
20. Shidham VB, Epple J. Appendix I: collection and processing of effusion fluids for cytopathologic evaluation, Chap. 14. In: Shidham VB, Atkinson BF, editors. Cytopathologic diagnosis of serous fluids: Elsevier (W. B. Saunders Company); 2007. p. 207–35.

20a. AV BioInnovation, NextGen CelBloking™ Kits. www.BioInnovation.com

21. Shidham VB. 'Cell blocks in Cytopathology' International Academy of Cytology. Workshop #5, May 17, 2010. http://www.slideshare.net/vshidham/cell-blocks-in-cytol-iac-wrkshp-i-5-1110-4057095?related=1.

21a. Shidham VB. CellBlockistry: Chemistry and art of cell-block making - A detailed review of various historical options with recent advances. CytoJournal. 2019;16:12.

22. Shidham V, Kampalath B, England J. Routine air drying of all the smears prepared during fine needle aspiration and intraoperative cytology studies: an opportunity to practice a unified protocol, offering the flexibility of choosing variety of staining methods. Acta Cytol. 2001;45:60–8.
23. Falk GW, Chittajallu R, Goldblum JR, Biscotti CV, Geisinger KR, Petras RE, et al. Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. Gastroenterology. 1997;112(6):1787–97.
24. Kadri SR, Lao-Sirieix P, O'Donovan M, Debiram I, Das M, Blazeby JM, et al. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. BMJ. 2010;341:c4372.
25. Hwang JH, Konda V, Abu Dayyeh BK, Chauhan SS, Enestvedt BK, Fujii-Lau LL, et al. Endoscopic mucosal resection. Prepared by: ASGE technology committee. Gastrointest Endosc. 2015;82:215.
26. Stewart CJR, Coldewey J, Stewart IS. Comparison of fine needle aspiration cytology and needle core biopsy in the diagnosis of radiologically detected abdominal lesions. J Clin Pathol. 2002;55(2):93–7.
27. Webb K, Hwang JH. Endoscopic ultrasound-fine needle aspiration versus core biopsy for the diagnosis of subepithelial tumors. Clin Endosc. 2013;46(5):441–4.

27a. Shidham VB, Dravid NV, Grover S, Kher AV. Role of scrape cytology in rapid intra-operative diagnosis- value & limitations. Acta Cytologica. 1984;28:477.

28. Shidham VB, Kajdacsy-Balla AA. Immunohistochemistry: diagnostic and prognostic applications, Chap. 47. In: Detrick B, Hamilton RG, Folds JD, editors. Manual of molecular and clinical laboratory immunology. 7th ed: American Society of Microbiology Press; 2006. p. 408–13. http://online.statref.com/titleinfo/fxid-274.html.
29. Shidham VB. Appendix II: immunocytochemistry of effusions processing and commonly used immunomarkers, Chap. 15. In: Shidham VB, Atkinson BF, editors. Cytopathologic diagnosis of serous fluids: Elsevier (W. B. Saunders Company); 2007. p. 237–57.
30. Phillips T, Simmons P, Inzunza HD, Cogswell J, Novotny J Jr, Taylor C, Zhang X. Development of an automated PD-L1 immunohistochemistry (IHC) assay for non–small cell lung cancer. Appl Immunohistochem Mol Morphol. 2015;23(8):541–9.
31. Lote H, Cafferkey C, Chau I. PD-1 and PD-L1 blockade in gastrointestinal malignancies. Cancer Treat Rev. 2015;41(10):893–903.
32. Wang J, Binder KR, Khatri R, Jaffee E, Laheru D. Immune therapy in GI malignancies: a review. JCO. 2015;60:7879.
33. Bhalla A, Zulfiqar M, Weindel M, Shidham VB. Molecular diagnostics in the neoplasms of small intestine and appendix. Clin Lab Med. 2013;33(4):861–6.
34. Zulfiqar M, Bhalla A, Weindel M, Shidham VB. Molecular diagnostics in esophageal and gastric neoplasms. Clin Lab Med. 2013;33(4):867–73.
35. Weindel M, Zulfiqar M, Bhalla A, Shidham VB. Molecular diagnostics in the neoplasms of the pancreas, liver, gall bladder, and extrahepatic biliary tract. Clin Lab Med. 2013;33(4):875–80.
36. Gouveia GR, Ferreira SC, Ferreira JE, Siqueira SA, Pereira J. Comparison of two methods of RNA extraction from formalin-fixed paraffin-embedded tissue specimens. Biomed Res Int. 2014;2014:151724, 5 pages.
37. RNAlater® Solutions for RNA Stabilization and Storage. Thermo Fisher Scientific. https://www.thermofisher.com/us/en/home/brands/product-brand/rnalater.html.

38. Cree IA, Deans Z, Ligtenberg MJ, Normanno N, Edsjö A, Rouleau E, et al., European Society of Pathology Task Force on Quality Assurance in Molecular Pathology; Royal College of Pathologists. Guidance for laboratories performing molecular pathology for cancer patients. J Clin Pathol. 2014;67:923–31.
39. Hunt JL. Molecular pathology in anatomic pathology practice: a review of basic principles. Arch Pathol Lab Med. 2008;132(2):248–60.
40. Netto GJ, Saad RD, Dysert PA II. Diagnostic molecular pathology: current techniques and clinical applications, part I. Proc (Bayl Univ Med Cent). 2003;16(4):379–83.
41. Netto GJ, Saad RD. Diagnostic molecular pathology. An increasingly indispensable tool for the practicing pathologist. Arch Pathol Lab Med. 2006;130:1339–48.
42. Fortna RR. Basic scientific principles of molecular pathology techniques (Northwest Pathology, Bellingham, WA, Presented on May 16, 2013). Webinar library, http://webinarlibrary.sakura-americas.com/basic-scientific-principles-of-molecular-pathology-techniques/.
43. Grada A, Weinbrecht K. Next-generation sequencing: methodology and application. J Investigative Dermatology. 2013;133:e11.
44. An Introduction to Next-Generation Sequencing Technology. Illumina. https://www.google.com/#q=next-generation+sequencing+methodology+and+application.
45. Rizzo JM, Buck MJ. Key principles and clinical applications of "next-generation" DNA sequencing. Cancer Prev Res. 2012;5(7):887–900.
46. Borrmann R. Geschwuelste des Magens und des Duodenums. Berlin: Springer; 1926.
47. Lewin KJ, Appelman HD. Tumors of the esophagus and stomach. Washington, DC: AFIP; 1996.
48. Redston M. Epithelial neoplasms of the large intestine. In: Odze RD, Goldblum JR, Crawford JM, editors. Surgical pathology of the GI tract, liver, biliary tract, and pancreas. Philadelphia: WB Saunders; 2004. p. 444–5.
49. Compton CC, Fielding LP, Burgart LJ, Conley B. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000;124:979–94.
50. Eisenberg B, Decosse JJ, Harford F, Michalek J. Carcinoma of the colon and rectum: the natural history reviewed in 1704 patients. Cancer. 1982;49(6):1131–4.
51. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003;58(6 Suppl):S3–43. http://www.worldendo.org/assets/downloads/pdf/parisclass/ParisClassification2000.pdf.
52. Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: classification, histology and application of molecular pathology. J Gastrointest Oncol. 2012;3(3):251–61.
53. Schlemper RJ, Hirata I, Dixon MF. The macroscopic classification of early neoplasia of the digestive tract. Endoscopy. 2002;34:163–8.
54. Hamilton SR, Aaltonen LA. Pathology and genetics of tumors of the digestive system. Lyon: IARC Press; 2000.. http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb2/BB2.pdf.
55. Gospodarowicz MK, Henson DE, Hutter RVP, O'Sullivan B, Sobin LH, Wittekind C, editors. Prognostic factors in cancer. 2nd ed. New York: Wiley-Liss; 2001.
56. Compton CC. College of American Pathologists. Practice protocols for the examination of specimens removed from patients with cancer. Northfield: College of American Pathologists; 1999.
57. Tuppurainen K, Makinen JM, Junttila O, Liakka A. Morphology and microsatellite instability in sporadic serrated and non-serrated colorectal cancer. J Pathol. 2005;207(3):285–94.
58. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
59. Fuchs CS, Mayer RJ. Gastric carcinoma. N Engl J Med. 1995;333(1):32–41.
60. Hase K, Shatney C, Johnson D, et al. Prognostic value of tumor "budding" in patients with colorectal cancer. Dis Colon Rectum. 1993;36(7):627–35.
61. Hase K, Shatney CH, Mochizuki H, Johnson DL. Long-term results of curative resection of "minimally invasive" colorectal cancer. Dis Colon Rectum. 1995;38(1):19–26.
62. Shinto E, Mochizuki H, Ueno H, Matsubara O, Jass JR. A novel classification of tumour budding in colorectal cancer based on the presence of cytoplasmic pseudofragments around budding foci. Histopathology. 2005;47(1):25–31.
63. Tanaka M, Hashiguchi Y, Ueno H, Hase K, Mochizuki H. Tumor budding at the invasive margin can predict patients at high risk of recurrence after curative surgery for stage II, T3 colon cancer. Dis Colon Rectum. 2003;46(8):1054–9.
64. Ueno H, Mochizuki H, Hatsuse K, Hase K, Yamamoto T. Indicators for treatment strategies of colorectal liver metastases. Ann Surg. 2000;231(1):59–66.
65. Ueno H, Murphy J, Jass JR, Mochizuki H, Talbot IC. Tumour 'budding' as an index to estimate the potential of aggressiveness in rectal cancer. Histopathology. 2002;40(2):127–32.
66. Jass JR, Atkin WS, Cuzick J, Bussey HJ. The grading of rectal cancer: historical perspectives and a multivariate analysis of 447 cases. Histopathology. 1986;10(5):437–59.
67. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol. 2005;23(3):609–18.
68. Xu LB, Wang J, Chao Liu C, Pang HW, Chen YJ, Ou QJ, Chen JS. Staging systems for predicting survival of patients with hepatocellular carcinoma after surgery. World J Gastroenterol. 2010;16(41):5257–62.
69. Shen SS, Haupt BX, Ro JY, Zhu J, Bailey HR, Schwartz MR. Number of lymph nodes examined and associated clinicopathologic factors in colorectal carcinoma. Arch Pathol Lab Med. 2009;133:781–6.
70. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al., National Cancer Institute Expert Panel. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst. 2001;93:583–96.
71. Compton CC. Pathology report in colon cancer: what is prognostically important? Dig Dis. 1999;17(2):67–79.
72. Dawson H, Kirsch R, Driman DK, Messenger DE, Assarzadegan N, Riddell RH. Optimizing the detection of venous invasion in colorectal cancer: the Ontario, Canada, experience and beyond. Front Oncol. 2014;4:354.
73. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: pathologic aspects. J Gastrointest Oncol. 2012;3(3):153–73.
74. Alexander J, Watanabe T, Wu TT, Rashid A, Li S, Hamilton SR. Histopathological identification of colon cancer with microsatellite instability. Am J Pathol. 2001;158(2):527535.
75. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321(5897):1801–6.

Pathological Evaluation, Classification, and Staging of Colorectal Cancers

3

Maryam Kherad Pezhouh and Elizabeth A. Montgomery

Pathological Evaluation

Sample Processing

It is important to be aware of the path that biopsied or resected tissue follows from the time it leaves the operating room or the endoscopy suite until the pathologist renders her diagnosis. Biopsy samples are usually submitted in containers with a chemical fixative such as formalin from the endoscopy suite so if studies that require fresh tissue are desired at the time of endoscopic biopsy, this must be arranged in advance with the endoscopist. However, many modern assays are standardized for use on formalin-fixed paraffin-embedded tissue. All specimens must be grossly (macroscopically) evaluated prior to processing for microscopic evaluation. Gross examination of a specimen or "grossing" is the inspection of the specimen with the naked eye to obtain diagnostic information and document precisely what was biopsied or resected from the patient. The first step in gross examination of a specimen is to confirm patient identity and the exact anatomical location from which the specimen was obtained. Whereas it is simple to identify the anatomic site of resection specimen that contains a segment of ileum, an appendix, and a length of colon, it is impossible to separate anatomic sites by gross evaluation of mucosal pinch biopsies, such that careful attention to labeling by the endoscopist is critical. The gross appearance of the specimen is documented and is included in the final pathology report.

M. K. Pezhouh (✉)
Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: maryam.pezhouh@northwestern.edu

E. A. Montgomery
Department of Pathology, Johns Hopkins University, Baltimore, MD, USA

Biopsy samples are typically small and submitted for processing "whole," whereas tissue from resection samples is cut with a razor blade into postage stamp-sized portions that fit in plastic cassettes that are processed to make paraffin tissue blocks. These tissue blocks are sectioned into 5- to 10-micron-thin sections positioned on glass slides for staining and microscopic examination. The histological sections are stained with the hematoxylin and eosin (H&E) stain for evaluation by a pathologist. In the vast majority of cases, an accurate interpretation can be made by the use of H&E stains alone.

Gross Evaluation of Small Biopsies and Large Polyps

Small colonic biopsies are minute fragments of tissue taken by pinch biopsy forceps. They typically measure from 0.5 mm to 3–4 mm, depending on the type of forceps used and the endoscopist. Gross evaluation of small biopsies includes recording the number of the fragments received and measuring the aggregate dimension and, in some instances, measuring the size of the largest fragment. Ideally, there should be no more than three fragments of tissue submitted per container. As the number of the tissue fragments increases on a slide, the possibility of unwanted error increases. Obviously, documenting the exact site from which the biopsy was obtained and documenting the type of tissue (such as polyp or mass versus flat mucosa) is essential for the pathologist to render the correct diagnosis.

Polyps removed during colonoscopy can be small or large, pedunculated or sessile. The cautery (diathermy) artifact identifies the resection margin in polyps removed with cauterized wire or hot polypectomy. Applying India ink to the stalk also can help the pathologist in identifying the margin of resection at the time of microscopic evaluation, as the applied India ink survives tissue processing and appears black on the glass slides. During pathological gross evaluation, the size, color, surface configuration, and appearance of

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_3

any base of a polyp and any visible stalk length should be documented. If the polyp is small (less than 1 cm), it is usually bisected and submitted in 1 cassette. Larger polyps are submitted in more cassettes. The stalk is first inked and then carefully cut and placed in different cassettes in order to evaluate for invasive carcinoma.

Gross Evaluation of a Resected Tumor

Resection specimen processing, not surprisingly, is more complicated than processing pinch biopsies. The first step in the gross examination after patient identification is to record the exact anatomical subdivision of the resected colon. We cannot emphasize enough the importance of correctly labeling the anatomical portion of the colon (e.g., sigmoid versus rectum versus rectosigmoid). Furthermore, it is impossible to distinguish the subdivisions of the colon, such as ascending versus transverse versus descending colon, by gross examination. Anatomically, serosa and taenia coli are present from the right colon until the sigmoid and are absent in the posterior rectum and anus. There is a serosal covering in the anterior upper rectum and the upper rectal sides. Mesentery, on the other hand, is absent in cecum and rectum and present in the transverse and sigmoid colon.

It is crucial for the pathologist to perform a careful gross examination of the external surface of the specimen and document any extension of tumor to the outer surface. Measuring the length and circumference of the specimen should be done before opening. The specimen should be received intact from the operating room. On rare occasions, some surgeons choose to open the colon in the operating suite. We strongly advise against it, as it may hamper pathological evaluation of the specimen including assessment of the depth of invasion (T stage) and the distance of the tumor from the margins (Table 3.1). For the concerned surgeon, issues of completeness of resection can usually be answered by the pathologist in the form of an intraoperative consultation.

Identifying the radial circumferential margin is a crucial step in grossing the rectal lesions. The rectosigmoid junction is where the peritoneum no longer completely surrounds the large bowel. The rectum is partially covered by peritoneum in the upper third (on the anterior and lateral sides) and in the middle third (only the anterior aspect). No peritoneum covers the lower third of the rectum. The exact location of the tumor must be identified and recorded. Thus, correctly labeling the specimen as rectal prompts the pathologist to identify the peritonealized versus nonperitonealized zones. Careful pathological grossing evaluation through orientation of the

Table 3.1 TNM staging of colorectal cancers

Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ*:* intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the musclaris propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures
Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the Subserosa Mesentery Nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive
Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs (this category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organ is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastasis

Table 3.1 (continued)

AJCC prognostic stage groups			
When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB
T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

specimen, inking, and evaluation of the margins allows assessment of completeness of the excision. The distance of the tumor to the closest margin, especially in the rectum, is an important prognostic factor. Ideally, in order to be able to properly section the specimen it is pinned to a corkboard or a wax board and fixed overnight in formalin. Representative sections of all of the components present (e.g., appendix, cecum, ascending colon) and any visible lesions are submitted for microscopic evaluation. The fat is stripped off of the specimen to identify all the lymph nodes.

Classification of the Colorectal Cancers and Precursor Lesions

Colorectal Polyps

Colonic polyps can be generally categorized as conventional adenomas or serrated polyps. Tubular or tubullovillous adenomas account for approximately 60% of colonic polyps. Serrated polyps are categorized as, hyperplastic polyps (HPs), sessile serrated adenoma (SSA), traditional serrated adenomas (TSAs), and SSA with cytological dysplasia (formerly termed mixed hyperplastic/adenomatous polyps [MHPAPs]). SSA with cytological dysplasia accounts for 1–2% of colonic polyps [1].

Tubular Adenoma

Tubular adenomas are considered precursor lesions to carcinomas. It is believed that about 10% of adenomas that are not removed will transform to adenocarcinomas [2]. Histologically, tubular adenomas are composed of cells with elongated pseudostratified hyperchromatic nuclei (Fig. 3.1). These nuclei maintain their polarity, meaning their long axis is perpendicular to the basement membrane (Fig. 3.2). Adenomas may contain scattered neutrophils, prominent apoptosis, Paneth cell differentiation, clear cell change, and squamous-like morules. Adenomas with so-called pseudoinvasion contain neoplastic glands that, together with their lamina propria, prolapse into the submucosa. These glands can become obstructed and the inspissated mucin can dissect through the tissue mimicking invasive carcinoma. In most

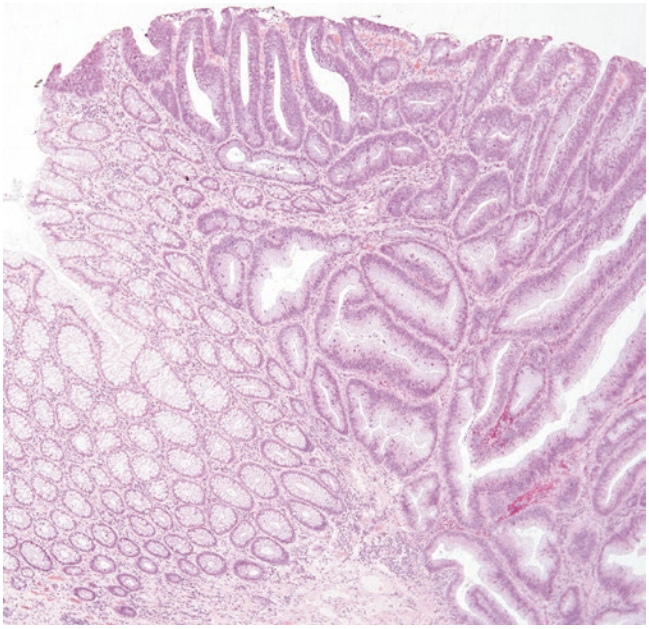


Fig. 3.1 Tubular adenoma. These polyps show hyperchromatic, pencil-like nuclei that remain perpendicular to the basement membrane (on the left) as compared to the normal mucosa (on the right)

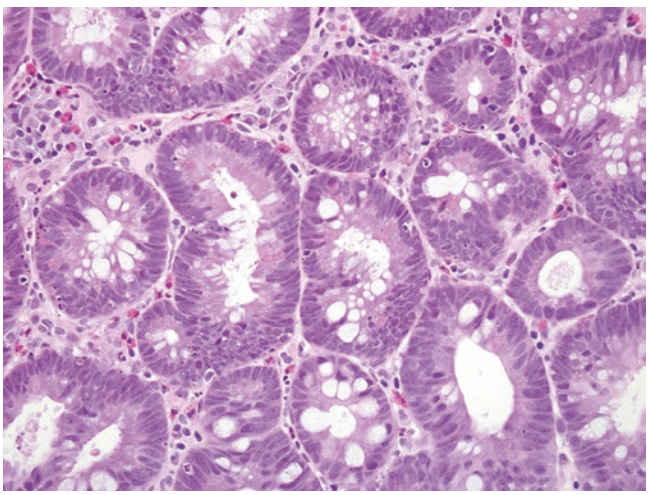


Fig. 3.2 Tubular adenoma. This figure highlights the elongated, hyperchromatic nuclei that are perpendicular to the basement membrane

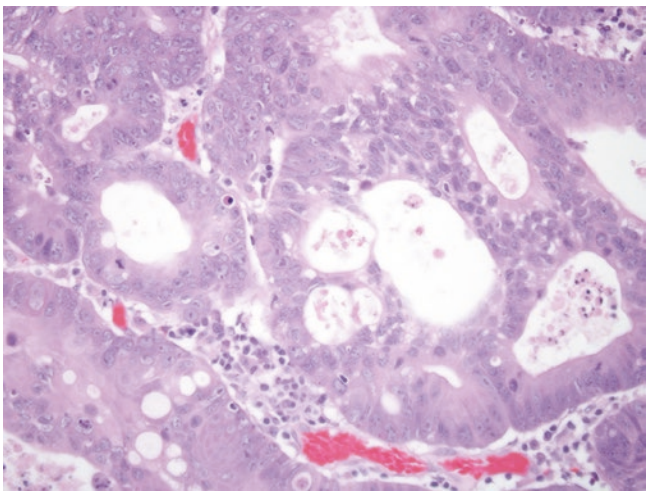


Fig. 3.3 Adenoma with high-grade dysplasia. This high-magnification image shows an area of cribriform architecture with loss of nuclear polarity and bizarre cells

cases, an expert pathologist can differentiate such pseudoinvasion from true invasion based on the presence of lamina propria, hemosiderin, round glands, and cytoarchitectural features.

Adenomas have low-grade dysplasia by definition. The presence of high-grade dysplasia in a tubular adenoma warrants a more frequent follow-up [3]. Cribriform architecture and/or loss of nuclear polarity along with cytological atypia and stratification of the nuclei to the surface or the gland lumina define high-grade dysplasia in an adenoma (Fig. 3.3). Intramucosal carcinoma happens when there is lamina propria invasion. Since the lamina propria of the colon lacks significant lymphatics, this early invasion is staged as Tis rather than T1 (submucosal invasion) (Table 3.1). In both occasions, whether there is high-grade dysplasia or intramucosal carcinoma in an adenoma, polypectomy should be curative. Tubulovillous adenomas show a mixture of tubular and villous architecture and villous adenoma is a polyp displaying predominantly villous architecture. Villous adenomas are believed to warrant closer surveillance than tubular adenomas, but the cutoff between the 2 is poorly defined.

Hyperplastic Polyps

Classical HPs are incidental findings during routine colonoscopy and account for the majority (about 75%) of all serrated polyps. They can be single or multiple, usually less than 5 mm, and commonly found in the rectosigmoid region. Histologically, they can be recognized as microvesicular, goblet cell-rich and mucin-poor variants. However, since these subtypes have no clinical significance, there is no need to subclassify them during routine histological examination.

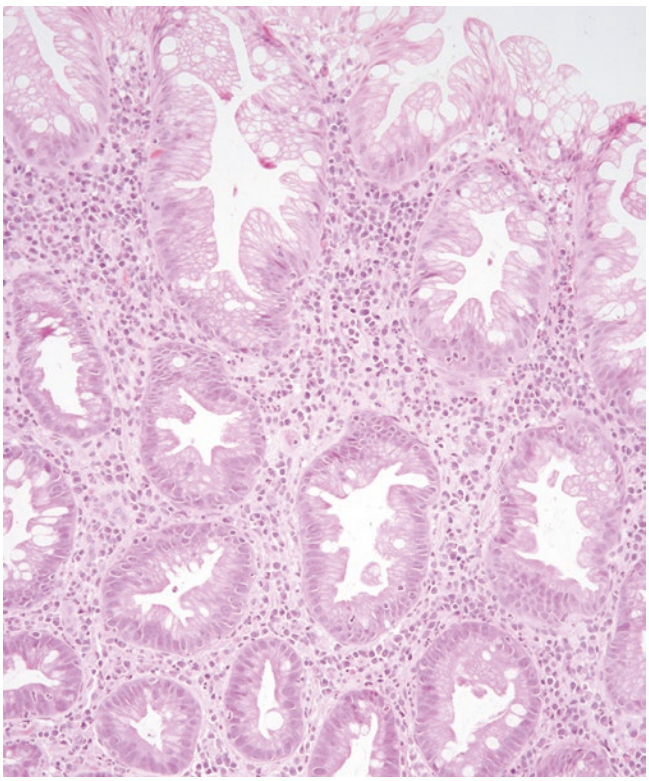


Fig. 3.4 Hyperplastic polyp. This example shows star-like glandular morphology in the upper crypts

Morphologically, HPs show serrated or star-like glandular morphology in the upper crypts with glands tapering down near the base with prominent neuroendocrine cells (Fig. 3.4). Some of these polyps might have a regular thickened collagen table. Microvesicular HPs have frequent BRAF mutation while goblet cell-rich HPs more commonly have KRAS mutation supporting the evidence of identifying and removing these polyps during endoscopy [1].

Sessile Serrated Adenoma/Sessile Serrated Polyp

Sessile serrated adenoma (SSA) and sessile serrated polyps (SSPs) account for 15–25% of all serrated polyps. Endoscopically, they may be subtle and difficult to distinguish from a thickened mucosal fold. They are broad-based and more commonly arise in the right colon and may attain a size of several centimeters. These polyps are characterized by serrated crypt architecture extending to the deep crypts with dilated crypt bases that are aligned parallel to the muscularis mucosae (Fig. 3.5). Morphological variability exists in these polyps. They can have oncocytic changes or increased or decreased mucin that sometimes resembles gastric foveolar epithelium. Conventional-appearing low-grade dysplasia can arise in SSA, characterized by loss of expression of MLH1 and/or PMS2 by immunohistochemistry.

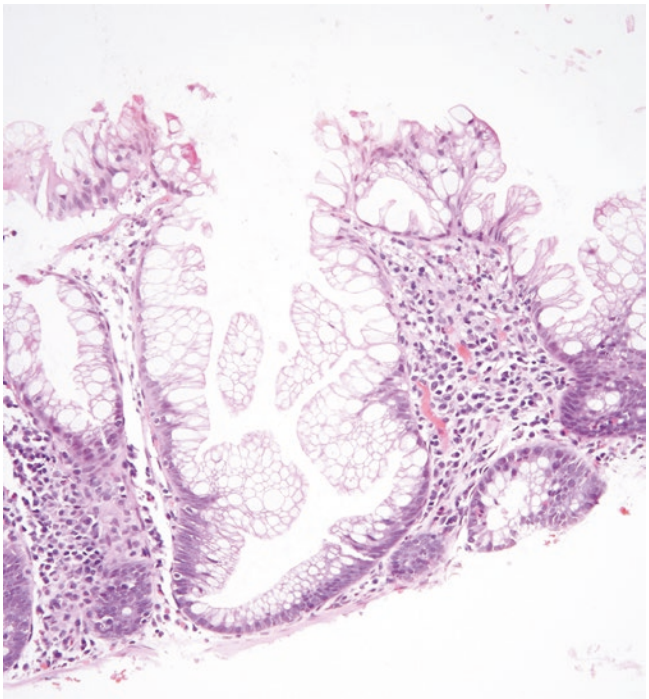


Fig. 3.5 Sessile serrated adenoma. Note the serrated crypt architecture extending to the deep crypts with a dilated crypt base aligned parallel to the muscularis mucosae

SSAs often harbor activating mutation in the *BRAF* gene, interfering with cellular apoptosis and thereby causing epithelial cells to accumulate over basement membrane producing serrated areas. Most SSAs (67%) have aberrant nuclear beta-catenin labeling, seen in the background of *BRAF* mutations and correlating with neoplastic progression [4].

Traditional Serrated Adenoma

Traditional serrated adenomas (TSAs) occur predominately in the distal colon. Histologically, these polyps are characterized by complex villiform architecture with crypts that lose their orientation to the muscularis mucosae and bud off disorganized glands (ectopic crypts). The lesional cells of TSA have brightly eosinophilic cytoplasm and cigar-shaped nuclei that are shorter than those of typical tubular adenoma (Fig. 3.6). These nuclei lack significant enlargement, prominent nucleoli and apoptosis. TSA are characterized by *KRAS* mutations and CpG island methylation, but they lack microsatellite instability (MSI) unlike SSAs that have progressed to dysplasia of carcinoma.

Filiform serrated adenoma is an uncommon variant of TSAs found on the left side of the colon. Complex delicate fronds, abundant eosinophilic cytoplasm and tiny crypts emanating from the surface of the fronds and edematous stroma characterize these polyps (Fig. 3.7). These polyps can be associated with areas of conventional tubular adenoma,

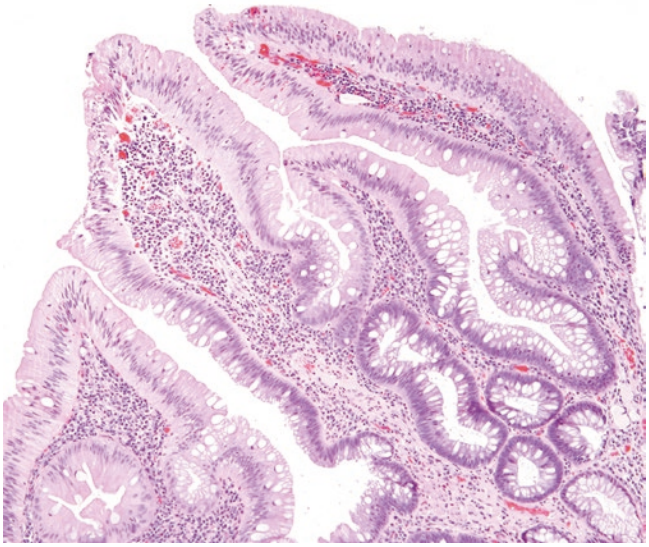


Fig. 3.6 Traditional serrated adenoma. This example shows the pink (eosinophilic) cytoplasm of these adenomas. Note the nuclei are smaller than those of a tubular adenoma

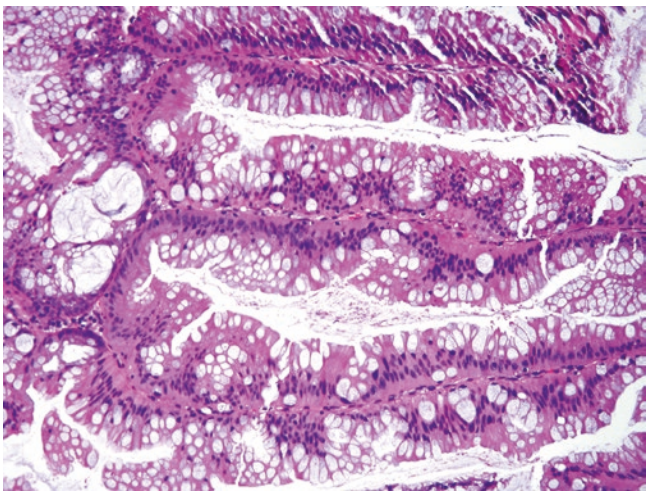


Fig. 3.7 Filiform serrated adenoma. Note the delicate fronds, abundant eosinophilic cytoplasm, and tiny crypts emanating from the surface of the fronds (ectopic crypts)

high-grade dysplasia, SSAs, or HPs. These polyps are molecularly similar to SSAs as they harbor *BRAF* mutation in approximately 50% and a minority with *KRAS* mutation around 21%. Filiform serrated adenomas are microsatellite stable or have low levels of microsatellite instability [5].

Malignant Adenoma (Adenocarcinoma in Adenoma, "Malignant Polyp")

Malignancy in adenomas or adenoma containing invasive carcinoma is defined by invasion of the tumor through the muscularis mucosae into the submucosa (Fig. 3.8). The

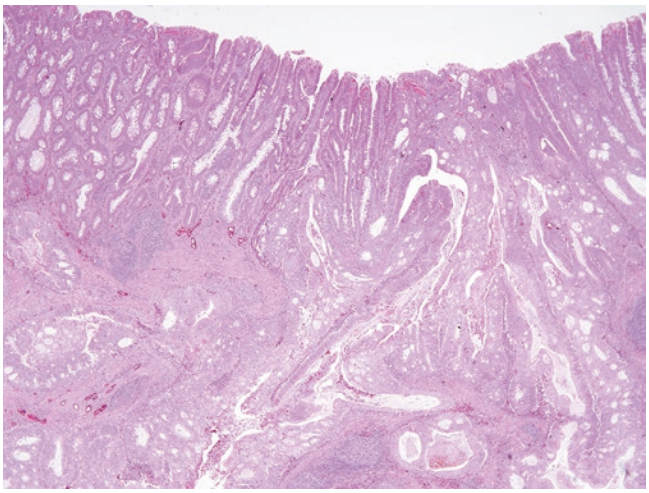


Fig. 3.8 Malignant adenoma (adenocarcinoma arising in association with an adenoma). Note the invasion of the tumor through the muscularis mucosae into the submucosa

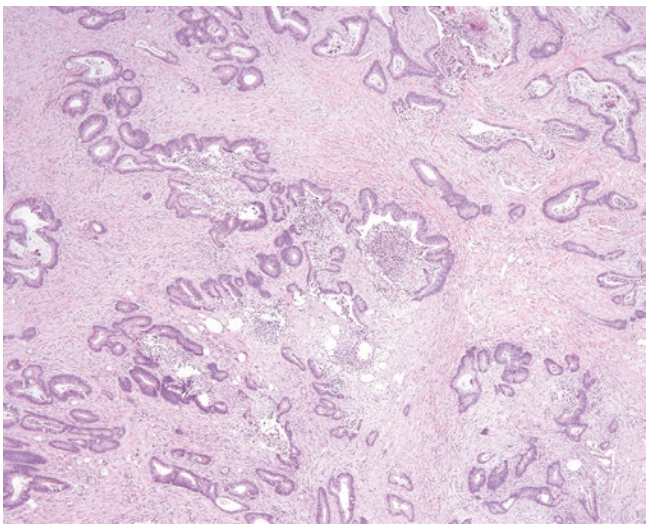


Fig. 3.9 Colonic adenocarcinoma. This example shows the angulated glands with central necrosis in a desmoplastic stroma

chance of finding an invasive carcinoma component in a polyp increases with increasing adenoma size. The likelihood of finding an invasive carcinoma component in an adenoma larger than 2 cm is approximately 35–53%. Ideally, large polyps should be resected intact (if possible) in order for the pathologist to be able to identify the margin of resection and asses the closet approach of tumor.

Many so-called malignant polyps are curable by endoscopic polypectomy alone. Criteria that have been offered to determine which such lesions require follow-up resection to harvest lymph nodes include: (1) high tumor grade, (2) tumor present ≤1 mm (or some references 2 mm) from the resection margin, and (3) small vessel invasion. Higher tumor grade includes poorly differentiated adenocarcinoma, signet ring cell carcinoma, small cell carcinoma or undifferentiated carcinoma and may be similar to so-called tumor budding. In the presence of any of these features, the risk of an adverse outcome is increased to 10–25% [6].

Colitis-Associated Dysplasia

Dysplasia in inflammatory bowel disease (IBD) is classified as low and high grade, and in unclear cases indefinite for dysplasia. The presence of active inflammation with reactive epithelial changes makes the diagnosis of low-grade dysplasia sometimes challenging in these patients. The diagnosis of low-grade dysplasia requires the presence of nuclear alteration extending to the surface epithelium. In contrast, high-grade dysplasia displays surface loss of nuclear polarity. Serrated epithelial changes also can be seen in these patients. A recent study demonstrated high frequency of dysplasia in the patients with serrated epithelial changes [7]. However, more studies are needed to determine if these serrated changes are precancerous.

There are some criteria to differentiate sporadic adenoma from polypoid colitis-associated dysplasia; however, no definite criteria exist for this distinction. Patients with polypoid colitis-associated dysplasia are usually younger (<50 years old) with duration of IBD more than 10 years and have active disease. Endoscopically, the polyps are ill defined versus the sporadic adenomas, which are usually well marginated. Histologically, polypoid-associated dysplasia display irregular gland configuration with a mixture of non-neoplastic and neoplastic glands and variable stroma, irregular mucin production, dystrophic goblet cells, and stratified nuclei in variable levels.

Colorectal Adenocarcinoma

The vast majority of colorectal adenocarcinomas can be diagnosed on a colonic mucosal biopsy with routine H&E staining. Histologically, colorectal adenocarcinomas are characterized by angulated glands and single cells with a desmoplastic stroma. These glands frequently contain necrotic debris, apoptosis, and scattered neutrophils (Fig. 3.9). As previously noted, submucosal invasion is necessary for the diagnosis of invasive adenocarcinoma. For obvious reasons, mucosal biopsies of the colon rarely contain abundant submucosa. However, the presence of well-developed desmoplasia in the lamina propria with associated invasion into the structure is almost invariably accompanied by an underlying invasive carcinoma that extends into at least the submucosa. Sometimes, in fragmented specimens, it is not possible to reach a diagnosis of adenocarcinoma. In cases for which we believe the invasion might be limited to the lamina propria, we report the findings as "at least intramucosal carcinoma/ invasion into the lamina propria/

Tis." Pathologists generally also report any associated adenoma component to note that the lesion is primary rather than a metastasis from another site.

Molecular Testing in Colorectal Carcinoma

Molecular testing can be performed on both biopsies and resection specimens. However, since staging is a factor in determining whether molecular testing is indicated, we often wait until the resection when staging data are available and there is abundant material for testing. Microsatellite instability (MSI) is generally performed for all patients under 70 with stage 1 tumors, all patients with stage 2 tumors, all patients under 70 with stage 3 tumors, and for all stage 4 tumors. Microsatellites or short tandem repeats (STRs) are repetitive DNA elements of 1–6 base units. These units are repeated 10–60 times, which creates inherent instability during replication. These errors are corrected through a system of DNA mismatch repair (MMR) in normal cells. Proteins encoded by the genes in this system, such as mutL homolog 1 (hMLH1), postmeiotic segregation increased 2 (hPMS2), mutS homolog1 (hMSH2), and mutS homolog 6 (hMSH6) genes.

There are some histological findings that are suggestive of MSI in colorectal tumors. These include intense lymphocytic intretumoral infiltrates (Fig. 3.10), mucinous (Fig. 3.11) or signet ring features, and Crohn-like peritumoral features. In fact, noting a combination of these features in a patient younger than 50 can predict MSI with great accuracy [8]. MSI testing involves microdissecting the tumor and the normal tissue from sections prepared from the paraffin-embedded tissue blocks and performing polymerase chain reaction (PCR) using primers directed to microsatellite markers. Therefore, we always encourage our clinical colleagues to also sample the normal mucosa in a young patient of less than 50 years old. However, this testing can be done later on the resected material where normal tissue is readily available. Different systems with different numbers of mononucleotides or dinucleotides marker are available for MMR testing. Several patterns of data interpretation exist: MSI-high (MSI-H), MSI-low (MSI-L), and microsatellite stable (MSS). When using 5 markers, MSI-H corresponds to greater or equal to 2 loci of MSI, when only 1 loci shows MSI is considered MSI-L and MSS is defined by no detected MSI.

Immunohistochemical staining is an alternative route to MMR testing. Pathologists can stain the tissue with surrogate markers for the presence of MMR gene mutations and such testing generally correlates well with MSI testing. MLH1, MSH2, MLH6 and PMS2 are the proteins encoded by the MMR genes and loss of immunolabeling will indicate a defective gene or, in the case of MLH1, inactivation of the gene by promotor methylation. Using immunohistochemistry also directs the clinician to order gene sequencing on the defective gene. As mentioned earlier, the lack of immunostaining does not preclude the possibility of inactivation of the gene by promotor methylation or a missense mutation that causes loss of function of the protein.

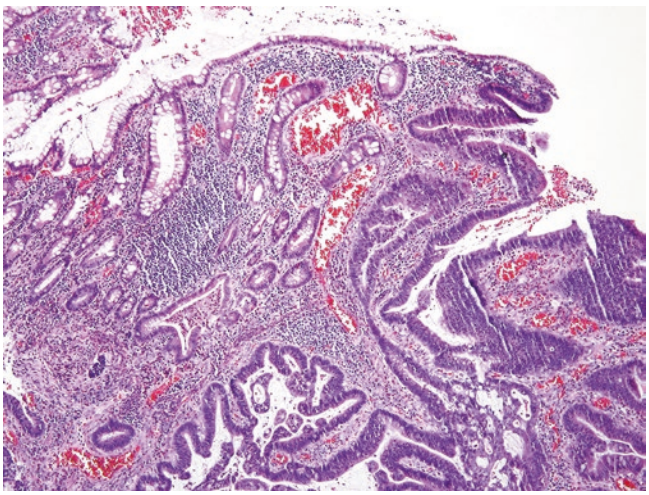


Fig. 3.10 Colon carcinoma associated with microsatellite instability (MSI). Note the presence of an adenocarcinoma with an intense lymphocytic infiltrate

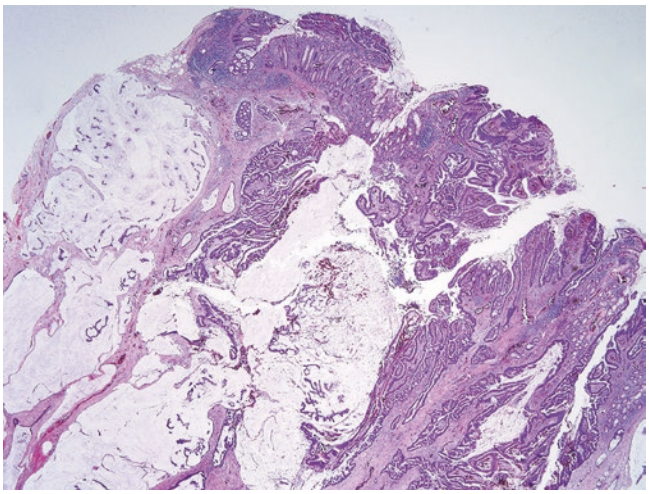


Fig. 3.11 Colon carcinoma associated with microsatellite instability (MSI). This an example of adenocarcinoma with mucinous features. Note the pools of mucin with floating malignant cells

Currently, *BRAF* and *KRAS* mutation status are commonly tested to guide therapeutic options as tumors that harbor these mutations are resistant to anti- epidermal growth factor receptor (EGFR) immunotherapy. Since these drugs are expensive and have significant morbidity, testing the gene is recommended. *KRAS* and *BRAF* mutational testing is indicated in any stage III or IV tumor; that is, any tumor that has spread to lymph nodes or distant sites. Common labora-

tory methods used are gene sequencing and real-time PCR. Many laboratories test the *KRAS* gene first and if it is mutated there is no need to test the *BRAF* gene, as the patient would be expected to be resistant to anti-EGFR therapy.

Hereditary Colorectal Cancer Syndromes

Familial Adenomatous Polyposis

Patients with familial adenomatous polyposis (FAP) have a germline mutation in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21 with complete penetrance, causing them to have hundreds to thousands of colonic adenomas (Fig. 3.12). These patients essentially all develop colon cancer without prophylactic colectomy. The proband usually manifests more than 100 or 1000 colonic adenomatous polyps. In these patients, polyposis is not limited to the colon and can involve the stomach and small bowel as well. Thus, even after colectomy, surveillance endoscopies of the upper tract are advised [9]. Morphologically, these tumors are indistinguishable from sporadic adenomas; and the earliest lesions consist of a single neoplastic crypt. The location of the mutation in *APC* gene affects the clinical phenotype that manifests. Thus, full gene sequencing is the standard diagnostic test. Early identification of individuals or their family members with the *APC* gene mutation allows for careful planning and early medical and surgical intervention prior to development of cancer.

Attenuated FAP is a similar dominantly inherited disease with high penetrance. Patients with this disease have fewer than 100 adenomatous colorectal polyps. The location of the *APC* gene mutation in these individuals is at the proximal or distal regions of the gene. Another *APC* gene mutation, I1307K mutation is a missense mutation most commonly found in Ashkenazi Jewish patients. This mutation is also dominantly inherited and increases the risk of developing colorectal cancer up to two- to fivefolds.

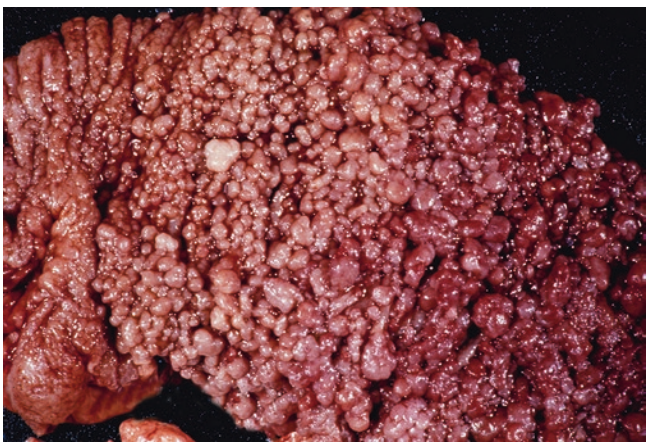


Fig. 3.12 Familial adenomatous polyposis. These patients may have hundreds to thousands of colonic adenomas

MutY-Associated Polyposis

Patients with MutY-associated polyposis have a phenotype similar to that of attenuated APC with less than 100 adenomatous polyps. However, this genetically distinct syndrome demonstrates an autosomal recessive mode of inheritance and is caused by mutation in the *hMYH* gene on chromosome 1.

Hereditary Nonpolyposis Colon Cancer/Lynch Syndrome

Hereditary nonpolyposis colon cancer (HNPCC)/Lynch syndrome accounts for 2–5% of all colorectal cancers and has an autosomal dominant mode of transmission with approximately 80–90% penetrance. The mutated genes in this syndrome are *MLH1* and *MSH2* followed by far fewer examples of mutations in *MSH6* and *PMS2*. Identification of an MMR gene mutation has significant impact on the entire family, leading to close screening and surveillance in those family members carrying the mutation. If a germline MMR mutation arises in a proband, the patient has Lynch syndrome. However, a minority of the colorectal cancers that are mismatch repair deficient are a result of Lynd syndrome. MSI is observed in about 15% of sporadic colorectal cancers mostly occurring in older individuals. Sporadic MSI-H is often due to promotor methylation of *MLH1*, silencing the MMR gene and resulting in loss of expression by immunohistochemistry and the presence of MSI. Thus, genetic testing to differentiate germline origin from sporadic origin is important to confirm Lynch syndrome. *BRAF* testing and MMR gene promotor methylation analysis also can be performed to differentiate sporadic versus germline mutation. MSI-H tumors harboring the *BRAF* V600E mutation are essentially always sporadic.

Serrated Polyposis Syndrome

The World Health Organization (WHO) defining criteria for diagnosing a serrated polyposis syndrome include: (1) the presence of 20 or more serrated polyps throughout the colon, or (2) at least 5 serrated polyps proximal to the sigmoid colon with 2 measuring more than 10 mm, or (3) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis.

Juvenile Polyposis Syndrome

Juvenile polyposis is characterized by more than 5 juvenile polyps in the colorectal region or the presence of multiple juvenile polyps throughout the gastrointestinal (GI) tract, or any number of these polyps in a patient with a family history of juvenile polyposis. These patients are at risk for colorectal, gastric, duodenal, and pancreatobilliary carcinomas. Juvenile-type polyps can be a component of several genetic syndromes such as juvenile polyposis, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome. Germline mutation in *DPC4* (also known as *SMAD4*) and *BMPR1A* predispose an individual to juvenile polyposis. Mutations in *PTEN,* a tumor suppressor gene, have been documented in Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. Although these syndromes have different mutations they share similar juvenile-type polyps. A combined syndrome of juvenile polyposis and hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) is described in patients with *SMAD4* mutations [10].

Sporadic juvenile polyps usually arise in children and usually have a spherical lobulated surface that is often eroded (Fig. 3.13). These polyps are considered hamartomatous. As such, when they arise in the colon they have colonic mucosa with irregularly shaped and dilated glands accompanied by lamina propria that is expanded by granulation tissue (Fig. 3.14). In syndromic patients, smaller polyps have the same features as sporadic juvenile polyps. However, the larger polyps display a relative increase in the epithelium compared to stroma with multilobulation or fingerlike lobes. These syndromic polyps can harbor true dysplasia (intraepithelial neoplasia) that can progress to carcinoma (Fig. 3.15). These polyps can show areas of erosion and active inflammation. Pathologists and clinicians should consider the possibility of these syndromic diseases when encountering nonspecific inflammatory polyps without associated prior mucosal injury. Of note, adult patients can develop inflammatory polyps that are presumably a result of prior mucosal injury and that can mimic juvenile polyps. Pathologists tend to report these cases as inflammatory/juvenile-type polyp.

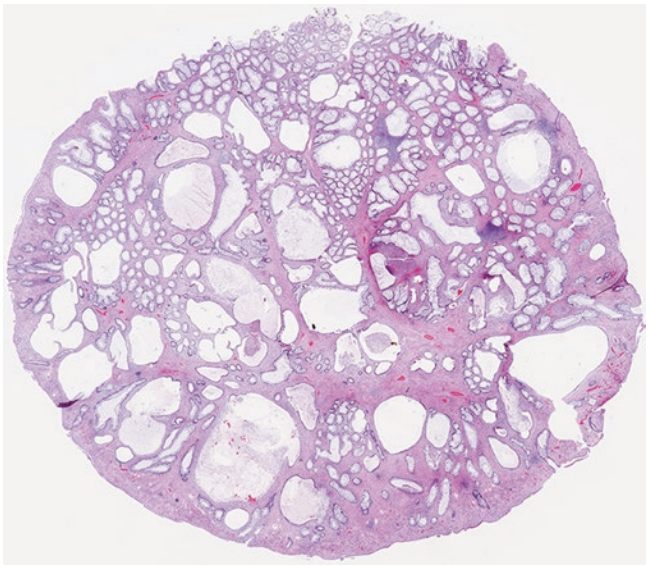


Fig. 3.14 Juvenile polyp. Microscopically, these polyps consist of numerous cystic and dilated glands with edematous stroma and associated lymphocytes and plasma cells

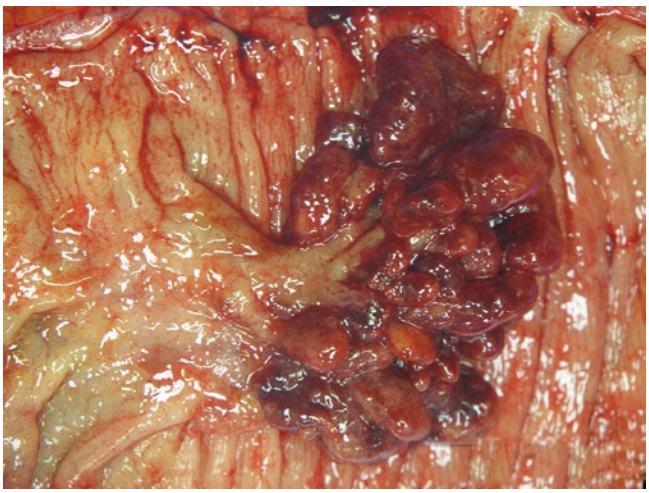


Fig. 3.13 Juvenile polyp. Gross examination of the resected colon shows a lobulated and pedunculated juvenile polyp

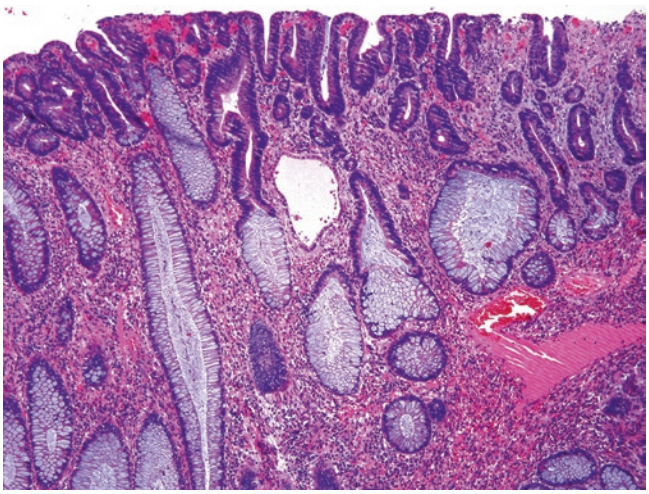


Fig. 3.15 Juvenile polyp with low-grade dysplasia. This example shows a juvenile polyp with low-grade dysplasia showing elongated pseudostratified hyperchromatic nuclei in the surface

Peutz-Jegher Syndrome

Peutz-Jegher (PJ) syndrome is an inherited cancer syndrome characterized by intestinal polyps and mucocutaneous melanin pigmentation. The most common malignancy in this syndrome is colorectal cancer followed by breast, small bowel, stomach, and pancreas carcinomas. Other extraintestinal malignancies arise in the endometrium, lung, ovary (sex cord tumors with annular tubules), cervix (adenoma malignum), and testis (Sertoli cell tumors). The average age at diagnosis of malignancies in patients with PJ syndrome is 42 years [11]. This syndrome is an autosomal dominant one with virtually 100% penetrance and is associated with mutation in the *LKB/STK11* gene in 80–94% of cases [12, 13]. The polyps in PJ syndrome are most common in the small intestine but can also arise in the colon and stomach.

Histologically, PJ polyps are hamartomatous and display the type of mucosa typical for the site in which they are found. Thus, in the stomach, they have gastric mucosa and in the colon they have colonic mucosa. These polyps characteristically display arborizing smooth muscle cores from which the mucosa leafs out (Fig. 3.16). The problem in diagnosing these polyps on mucosal biopsies arises when biopsies are superficial or when ulceration distorts the architecture. In the colorectal region, mucosal prolapse is very common and characterized by the presence of smooth muscle in the lamina propria and thus, it is difficult to prospectively diagnose PJ syndrome based on a colonic polyp in isolation. This diagnosis should be made in the context of clinical history. Although these polyps can have dysplasia or associated invasive carcinoma [14], most GI malignancies do not arise from the polyps themselves.

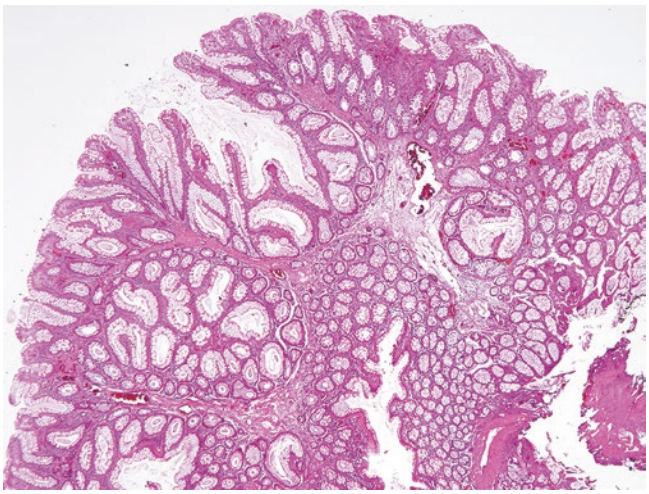


Fig. 3.16 Peutz-Jegher polyp. Note the arborizing smooth muscle separating groups of glands

Cronkhite-Canada Polyps

Cronkhite and Canada first reported this syndrome in 1955 in a series of patients with polyposis, pigmentation, alopecia, and onychotrophia [15]. Several studies afterward were able to further characterize this syndrome; however, the polyps arising in Cronkhite-Canada syndrome are impossible to prospectively diagnose based on microscopic features in isolation [16]. Cronkhite-Canada syndrome is characterized by diffuse polyposis in patients with unusual ectodermal abnormalities, including alopecia, onychodystrophy, and skin hyperpigmentation. The mean age of onset is around 59 years with a male-to-female ratio of 3:2, and it has been reported mostly in Southeast Asians and Europeans. This syndrome can have fatal complications such as malnutrition, GI hemorrhage, and infection, with a mortality rate as high as 60%. The most common presenting symptoms include diarrhea, weight loss, hypogeusia, and anorexia. Paraesthesias, seizures, and tetany have also been recorded. The poor outcome of these patients reflects a number of complications such as fatal GI bleeding, intussusception, prolapse, and malabsorption leading to malnutrition and recurrent infections.

Cronkhite-Canada syndrome is distinguished by the diffuse distribution of the polyps throughout the gastrointestinal tract sparing only the esophagus. It remains controversial whether these polyps have malignant potential. Histologically, broad sessile bases, expanded edematous lamina propria and cystic glands characterize these polyps. These features also can be seen in juvenile polyposis. Additionally, the polyps of Cronkhite-Canada have a pedunculated growth pattern except in the stomach. Clinical correlation with the ectodermal findings is helpful in diagnosing these polyps. Furthermore, if the endoscopist biopsies the flat mucosa in between polyps, it is normal in juvenile polyposis syndrome whereas it is abnormal in Cronkhite-Canada syndrome. The presence of dysplasia favors juvenile polyposis as essentially all Cronkhite-Canada polyps are nondysplastic.

Neuroendocrine Tumors

Most well-differentiated neuroendocrine tumors occur in the GI tract. In the large bowel, they are essentially limited to the rectum [17]. Rectal neuroendocrine tumors are more common in African Americans and Asians and slightly more common in males than females. A small percentage of GI tract neuroendocrine tumors are reported in the ascending colon, most commonly in the cecum. In contrast to the rectal neuroendocrine tumors, the tumors reported in the right colon are nonlocalized in 55–67% and most patients (85%) have metastatic disease at the time of presentation [17, 18].

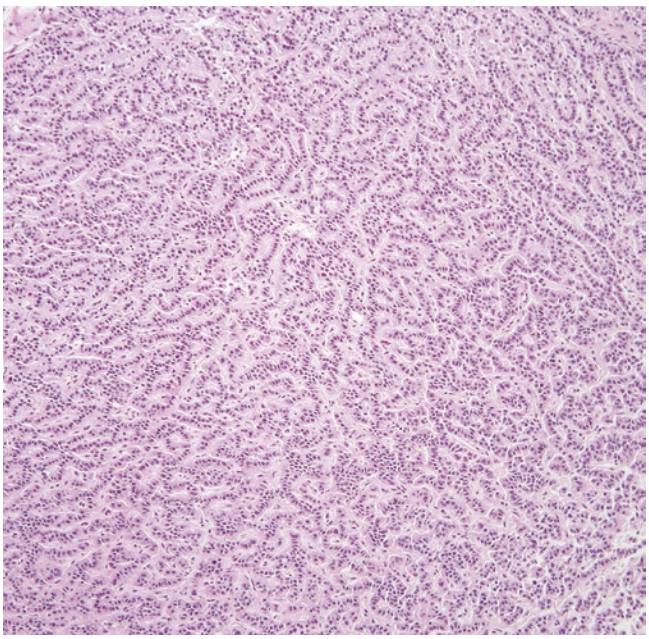


Fig. 3.17 Well-differentiated neuroendocrine tumor. This example has a trabecular growth pattern

Neuroendocrine tumors are classified as well-differentiated and poorly differentiated tumors. Well-differentiated tumors are further divided into G1 or carcinoid tumors and G2 or intermediate. Poorly differentiated neuroendocrine tumors are characterized as G3 (large and small cell type). Histologically, grade 1 and grade 2 tumors are composed of uniform cells arranged in an insular, trabecular, solid, or cribriform pattern (Fig. 3.17). The cells have moderate amount of cytoplasm with round, regular nuclei with a so-called salt-and-pepper chromatin pattern. These lesional cells can frequently form rosettes. The WHO grading system is used for neuroendocrine tumors in the stomach, duodenum, pancreas, and hindgut (colorectal region). This grading system is based on number of mitosis per 10 high power field (HPF) or percentage of MIB1/Ki-67 immunolabeling in lesional cells. G1 is defined based on less than 2 mitoses per 10 HPF or less than 2% Ki67 index. G2 is for mitotic counts between 2 and 20 per 10 HPF or a Ki-67 immunolabeling of 3–20%. Grade 3 tumors are high-grade neuroendocrine carcinomas with small or large cell histology and are characterized by more than 20 mitosis per 10 HPF or more than 20% ki-67 index.

Most well-differentiated neuroendocrine tumors of the rectum are small and localized at the time of presentation and detected at the time of screening colonoscopy. These tumors behave in an indolent fashion and the associated 5-year survival is 90%. Tumor size and invasion of muscularis propria are the two most important predictors of malignant behavior. Small tumors, 1 cm to 2 cm without muscularis propria invasion can be managed by polypectomy. However, even small tumors (between 1 cm and 2 cm) that invade the muscularis propria require transanal excision [17, 19]. Neuroendocrine tumors larger than 2 cm or with regional lymph node involvement are surgically managed as per rectal adenocarcinoma.

Neuroendocrine carcinomas are associated with extensive necrosis, apoptosis, and lymphovascular invasion. The small cell type demonstrates a diffuse growth pattern with round nuclei and nuclear molding. Large cell neuroendocrine tumors usually show a nested pattern of growth with round to oval cells with moderate amount of cytoplasm, granular or vesicular chromatin pattern and visible nucleoli. These tumors can have focal lumen formation and in some instances intracytoplasmic mucin. Of note, high-grade neuroendocrine carcinomas are frequently associated with an adenoma or conventional adenocarcinoma component. Neuroendocrine carcinomas (G3) are aggressive tumors with poor prognosis; however, there is no significant difference between small cell and large cell subtype [20]. Neuroendocrine tumors usually express keratin, synaptophysin, and chromogranin by immunohistochemistry.

Colorectal Sarcomas

Sarcomas of the colon and rectum are very rare and comprise less than 0.1% of all the cancers in this region [21]. Leiomyosarcoma is the most common type of colorectal sarcomas and account for more than 95% [22]. Other sarcomas encountered in this region include Kaposi sarcoma [23], fibrosarcoma [24, 25], angiosarcoma [25], and lipoleiomyosarcomas [26].

Leiomyosarcoma

Most of the colorectal leiomyosarcomas occur in men in the fifth and sixth decade with a predilection for black patients [27]. However, there are case reports of leiomyosarcoma in infants [28]. Histologically, these tumors have perfectly perpendicular fascicles of spindle cells with pleomorphic blunt-ended nuclei with increase abnormal frequent mitosis (Figs. 3.18 and 3.19). Pathologists must differentiate them from gastrointestinal stromal tumors (GISTs), which is easily done by performing immunohistochemistry. Leiomyosarcomas express desmin and not CD117 in contrast to GIST. They also have a better outcome than rectal GIST [29]. Surgical resection is the mainstay of treatment [27].

Kaposi Sarcoma

Kaposi sarcoma (KS) is a quasi-neoplastic sarcoma-like lesion usually encountered in patients with human

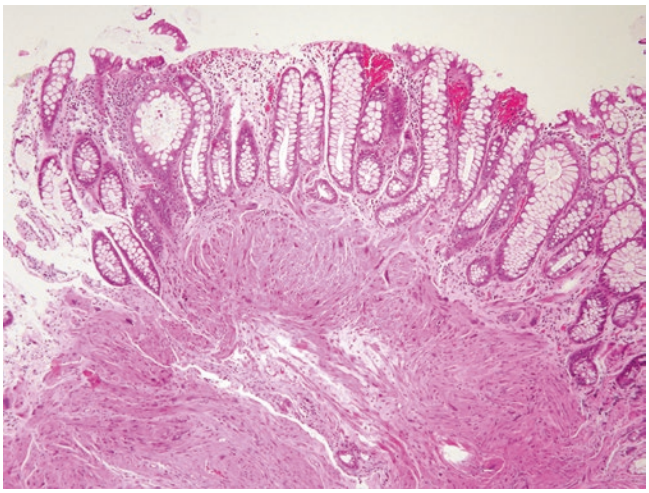


Fig. 3.18 Leiomyosarcoma. This example is extending into the lamina propria and consists of fascicles of spindle cells

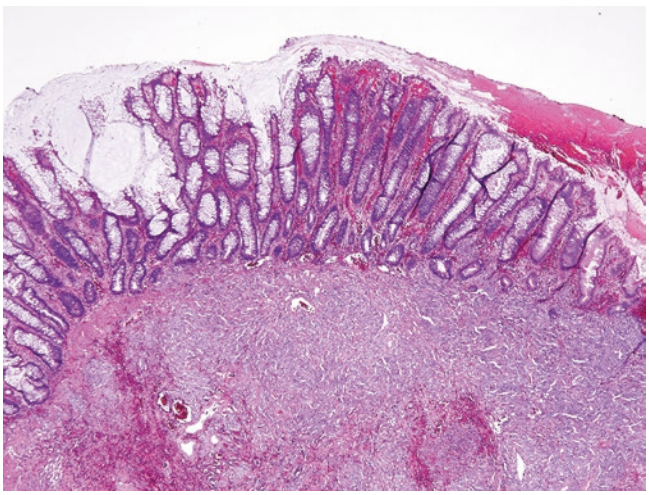


Fig. 3.20 Kaposi sarcoma. This tumor is composed of relatively monomorphic spindled cells, with slit-like vascular channels containing red blood cells

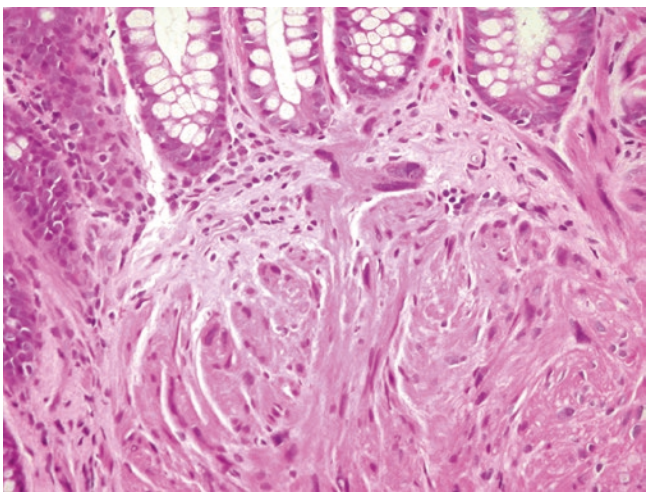


Fig. 3.19 Leiomyosarcoma. This high-magnification image shows the pleomorphic blunt-ended nuclei of a leiomyosarcoma

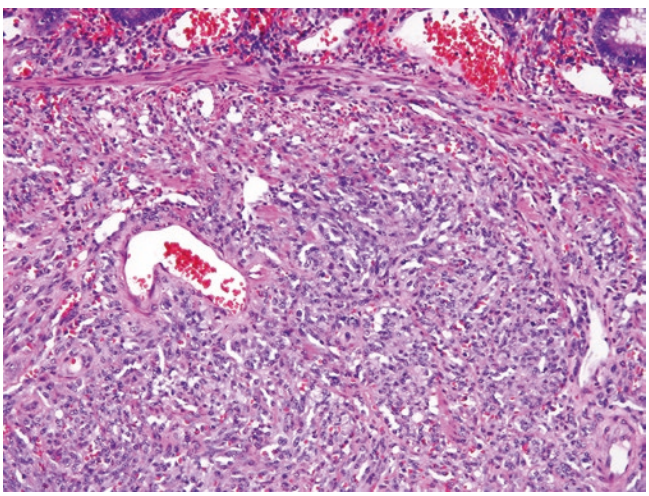


Fig. 3.21 Kaposi sarcoma. This is a higher magnification image of a Kaposi sarcoma highlighting the spindle cells with slit-like vascular channels and erythrocytes

immunodeficiency virus (HIV). KS often involves the skin and lymph nodes, but also can occur throughout the GI tract, including in the rectum and anus. Approximately 40–50% of the HIV patients with cutaneous KS lesions have concurrent lesions in their GI tracts [23]. Rectal KS most often occurs in men who have sex with men (MSM) with HIV with the average age of 34 years [30]. Patients with KS of the GI tract are usually asymptomatic but can have bleeding, diarrhea, or proctalgia. Microscopically, KS is composed of bland spindle cells with prominent red blood cell extravasation (Figs. 3.20 and 3.21). On immunolabeling, the spindle cells express CD34 and CD31 and the diagnosis can be confirmed by demonstration of expression of HHV8 using LAN-1 immunolabeling. Radiation remains the treatment of choice in these patients [21].

Gastrointestinal Stromal Tumors of the Colon

The most common location for GIST in the GI system is the stomach; however, in the lower GI tract region, it often arises in the rectosigmoid colon. They can present with abdominal pain or mass effect. They are usually transmural tumors with intraluminal or outward bulging. Rarely, they can present as subserosal lesions. Histologically, most GISTs are composed of spindle cells in fascicles, palisading with a storiform arrangement or an organoid pattern (Fig. 3.22). Some GISTs can have epithelioid cells as well. By immunohistochemistry, most colonic GISTs are CD117, DOG1, and CD34 positive. Risk assessment of GIST is based on the site, size, and mitotic activity. These tumors are not routinely encountered

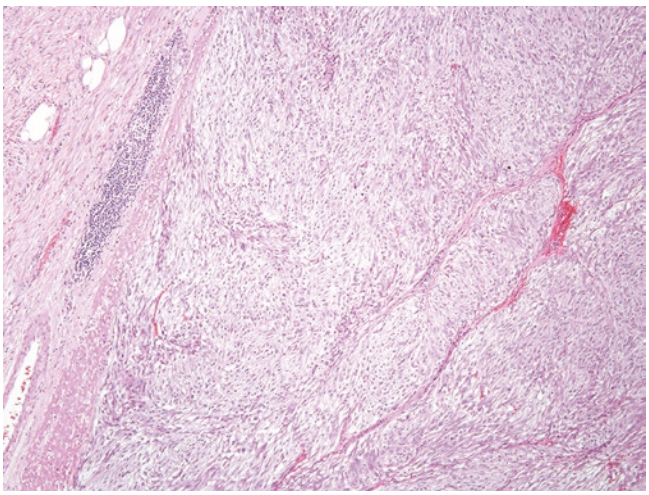


Fig. 3.22 Gastrointestinal stromal tumor (GIST). The tumor consists of monotonous spindle cells arranged in fascicles

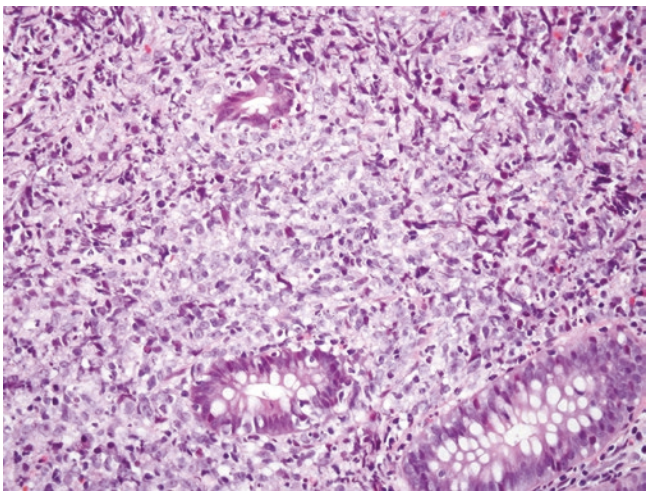


Fig. 3.23 Diffuse large B-cell lymphoma. This example shows the large neoplastic lymphoid cells in the colonic mucosa with apoptosis and inflammatory infiltrate

on colonic biopsies, as they are often transmural. Tumors that invade the mucosa have a worse prognosis.

Lymphoma

Lymphomas are more commonly encountered in the small intestine than the colon or rectum. In the colon, the 2 most common sites of involvement are the cecum and rectosigmoid [31]. Leukemias can also involve the right colon and present with an ischemic colitis pattern.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype affecting the colon. Patients who are immunosuppressed due to HIV, inflammatory bowel disease, and transplantation are at higher risk for lymphomas. Patients with colonic lymphomas can present with abdominal pain, anorexia, weight loss, obstruction, a palpable mass, perforation, or hematochezia [31–33]. Endoscopically, lymphomas manifest as fungating tumors, infiltrative processes, or as ulcerative lesions. Histologically, DLBCL is composed of large cells up to 5 times the size of a normal lymphocyte, with apoptosis and an inflammatory infiltrate (Fig. 3.23). The neoplastic cells can express B-cell markers by immunohistochemistry such as CD19, CD20, CD22, and CD79a. They can also have variable expression of the following antigens: CD10, BCL6, and MUM1.

Follicular Lymphoma

Follicular lymphoma can involve the ileocecal and ascending colon. It can present as multiple mucosal polyps up to 1 cm

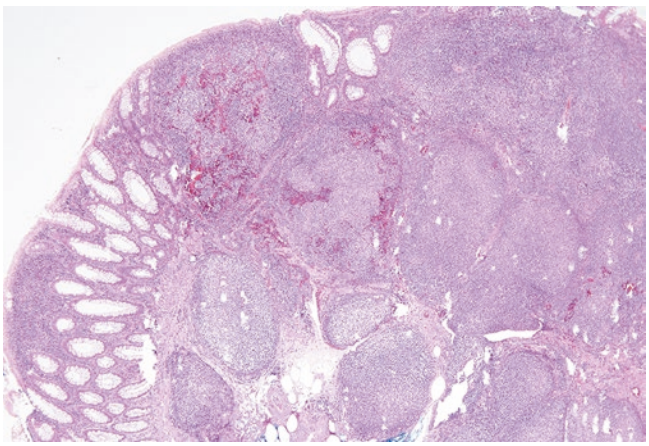


Fig. 3.24 Follicular lymphoma. This example shows the colonic mucosa with exaggerated lymphoid follicles and monotonous germinal centers

[34, 35]. Morphologically, follicular lymphoma presents with exaggerated lymphoid follicles with monotonous germinal centers without typical tingible body macrophages (Fig. 3.24). Most cases are low grade with low mitotic activity. The lesional cells coexpress CD20, CD10, and BCL6 and aberrantly express BCL2 by immunolabeling.

Extranodal Marginal Zone Lymphoma

Mucosal-associated lymphoid tissue (MALT) lymphoma or extranodal marginal zone lymphoma can present as multiple mucosal polyps like mantle cell and follicular lymphoma [35, 36]. Patients can be asymptomatic or present with abdominal discomfort [36]. Histologically, this type of lymphoma is composed of small-to-intermediate size lymphocytes with indented nuclei and abundant cytoplasm involving

the mucosa and submucosa. Immunohistochemically these cells coexpress CD20 and CD43 in 50% of the cases and are negative for CD5, CD10, and CyclinD1. MALT lymphoma has a favorable prognosis and a long-term disease-free survival.

Burkitt Lymphoma

Burkitt lymphoma (BL) is an aggressive B-cell lymphoma that can involve the GI tract, most commonly the ileocecal region and less often the stomach and rectum. BL occurs in 3 clinical forms: (1) endemic, (2) sporadic, and (3) immunodeficiency associated. All 3 forms can present as a bulky mass-forming lesion in the GI tract. Lymph nodes are usually not involved but encased with tumor. Touch imprints and smears can be helpful in diagnosis as the imprint is distinct. The cells on the cytology preparation have deeply blue cytoplasm with lipid vacuoles. Morphologically, the classical and endemic BL is characterized by a "starry sky" appearance composed of sheets of medium size cells (the sky) and scattered tangible body macrophages (the stars). The cells may show squared-off borders with round nuclei and multiple basophilic nucleoli. The atypical pattern has more pleomorphism and fewer nucleoli compared to the classical type. These tumor cells express CD20 and CD10 and lack CD5, BCL2, and TdT. K-i67 immunolabeling shows a very high proliferative index with nearly 100% of the cells being positive.

T-Cell Lymphoma

T-cell lymphoma of the GI tract is rare, principally affecting the small intestine in the setting of gluten sensitive enteropathy [37]. Some cases of primary colonic T-cell lymphoma of the colon have been reported in the Japanese literature in patients with ulcerative colitis [38, 39]. Rare Western cases reported have been associated with gluten sensitive enteropathy [37, 39]. Colonic T-cell lymphoma may present as multiple polyps or multiple shallow or deep ulcers with or without luminal narrowing. Tumor cells are composed of medium-to-large cells with significant cellular pleomorphism, irregular nuclei with small nucleoli and scant-to-moderate amounts of cytoplasm. The tumor cells usually are CD3+, CD4−, CD7+, CD8−, and CD56− and express cytotoxic granule-associated protein TIA-1 often with granzyme B.

Intravascular Lymphoma

Intravascular lymphoma (IVL) or angiotrophic lymphoma is a non-Hodgkin lymphoma that proliferates within the small- and medium-sized blood vessels. IVL usually involves the skin and central nervous system but rarely can affect the lymph nodes, bone marrow, and colorectal region. IVL patients with GI tract involvement present with abdominal pain as a result of bowel ischemia. Colonic biopsies from such patients display ischemic necrosis of the bowel wall with associated vessels containing neoplastic lymphoid cells [40].

Primary Effusion Lymphoma

Primary effusion lymphoma (PEL) is an HHV8-driven lymphoma that usually involves the body cavities in HIV-positive patients. Patients can present with pleural effusion, ascites, and pericardial effusion. In HIV-positive patients, it can accompany Kaposi sarcoma. This neoplasm can rarely present as a solid mass and can involve any part of the GI tract. Morphologically, it is composed of large anaplastic cells with ovoid to irregular nuclei, open chromatin, prominent nucleoli, and moderate amount of pale blue cytoplasm [41]. All cases are positive for HHV8/LAN-1 by immunohistochemistry. Furthermore, these lesional cells are positive for CD45, CD30, and CD138 (plasma cell marker) and are negative for some B-cell markers (such as CD20−, CD19−) and some T-cell markers (CD3− and CD4−). Most cases associated with HIV are coinfected with Epstein-Barr virus (EBV) that can be demonstrated by Epstein-Barr encoding region (EBER) in situ hybridization. These patients with extracavitary PEL have a poor prognosis.

Hodgkin's Lymphoma

Hodgkin's lymphoma can also be encountered in the GI tract; however, the diagnosis should be made with caution. It has been reported in patients with IBD treated with immunomodulation.

Other Tumors

Tumors outside of the colorectal region can either extend or metastasize to the area. These tumors include prostate and bladder carcinoma, tumors of the lung, breast, ovary, and stomach as well as melanoma (Fig. 3.25), mesothelioma, endometrial stromal sarcoma, and hepatocellular carcinoma. Metastatic breast carcinoma in the colon can mimic primary signet ring cell carcinoma. When poorly differentiated carcinoma is encountered in the colorectal region, one should always consider metastatic breast carcinoma in women and direct spread from prostate cancer in men.

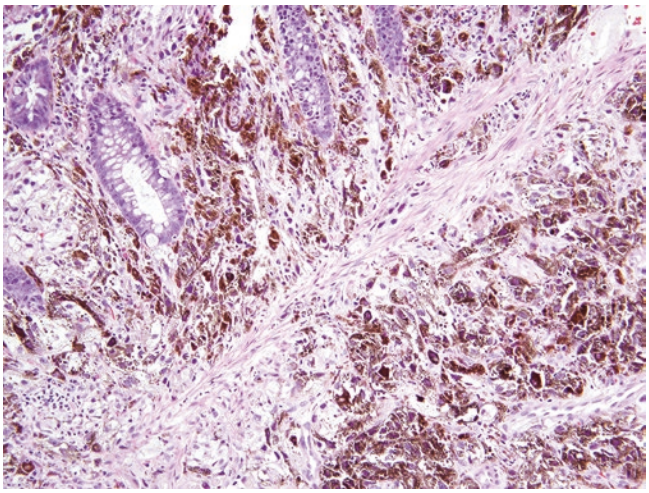


Fig. 3.25 Melanoma. This example shows atypical melanocytes with abundant melanin pigment infiltrating the colonic mucosa and extending into the submucosa

Colorectal Cancer Staging

The purpose of cancer staging is to document the extent of the cancer and is a crucial element to determine the appropriate course of treatment based on the data concerning outcome of patients with similar stage lesions. It also facilitates treatment evaluation, exchange, and comparison of results between different institutions and serves as a basis for cancer research. Several different cancer staging systems are currently used worldwide. However, the tumor node metastasis system (TNM) is the most clinically useful and is discussed here [42]. The American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) maintain this system collaboratively. Classification of the tumors by TNM system is based on the size and extent of the primary tumor (T), regional lymph node (N) status, and the presence or absence of the distant metastasis (M) (Table 3.1). Recently, nonanatomic prognostic factors have begun to supplement this cancer staging system.

Most cancers of the colorectal region are staged after surgical resection of the tumor. In this region, the depth of tumor invasion into or beyond the wall of the intestine and invasion or adherence to adjacent organs or structures is also defined by T. The number of lymph nodes involved (N) and presence or absence of distant metastasis (M) are the other features of the TNM staging system. In patients who receive neoadjuvant chemotherapy before the surgical resection a "y" prefix is added to the pathological staging. The TNM staging system for the colorectal region can be used for all the carcinomas arising in this region; however, well-differentiated neuroendocrine tumors of the colon and rectum are staged separately.

The large intestine or colorectum is divided into the cecum, the right or ascending colon, the middle or transverse colon, the left or descending colon, the sigmoid colon and the rectum. The cecum is the blind pouch that connects the terminal ileum to ascending colon and is covered with a visceral peritoneum (serosa). The posterior surface of ascending and descending colon lack the serosa and are in direct contact with the retroperitoneum. The transverse colon is intraperitoneal and is entirely covered by serosa attached to the pancreas by a mesentery. The sigmoid colon is also entirely intraperitoneal and covered by serosa. The rectum is covered by serosa on the anterior side to the middle third and on the lateral walls to upper third. The posterior surface of the rectum lacks serosa. The distal third of the rectum also known as the rectal ampulla has no peritoneal covering. The anal canal extends from the rectum to the anal verge and is 3–5 cm in length.

Lymph nodes are located along the major vessels supplying the colorectal region, adjacent to the colon and also along the arcades of the marginal artery. The number of lymph nodes sampled should be recorded, as it is important prognostically and is associated with increased accuracy in staging the tumor. At least 10 to 14 lymph nodes should be sampled in radical colectomy specimens. However, fewer lymph nodes may be removed or found in patients who have undergone radiation prior to surgical resection. Carcinomas of the colon can metastasize to any organ but the liver and lung are the most commonly affected. Seeding of other segments of the colon, small intestine, and peritoneum can also occur.

Clinical Staging

This staging is based on the medical history, physical examination, and colonoscopy with biopsies. Radiographic evaluations to be done to evaluate extracolonic or extrarectal spread include computed tomography (CT scan of abdomen, chest, and pelvis), magnetic resonance imaging (MRI), and positron emission tomography (PET) or fused PET/CT. Patients with rectal cancer might need a preoperative adjuvant treatment based on the pelvic extent of the disease combined with absence of extra pelvic metastasis. Pelvic MRI alone or with endorectalcoli, pelvic CT, or endoscopic ultrasound can be used to evaluate the pelvic extent of the disease. To evaluate the nodal staging, ultrasound-guided fine needle aspiration (FNA) of the lymph nodes can improve the accuracy. It is important to assign a clinical TNM staging (cTNM) prior to initiating preoperative therapy.

Pathological Staging

Most cancers of the colon and rectum are pathologically staged after surgical resection of the tumor (pTNM). For

patients who were assigned a clinical staging (cTNM) prior to the initiation of the adjuvant therapy, a modified pathological staging is implemented (ypTNM).

Carcinoma in situ (pTis) is defined by cancer cells present within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) without invasion of the submucosa. Carcinoma in situ of the large intestine has no risk of metastasis. Carcinoma in a polyp is classified with the same principle and was discussed earlier. That is, if the carcinoma cells are within the epithelium or lamina propria, it is considered carcinoma in situ; however, invasion of the submucosa of the polyp head or stalk is considered as pT1. Tumors that invade the muscularis propria are classified as pT2 and when the carcinoma cells invade through the muscularis propria and involve the pericolorectal tissues is assigned to the pT3 category. Tumors that have directly extended and involved the visceral peritoneum, or are histologically adherent to other organs or structures, are classified as pT4. Since tumors in this category have a different prognosis based on the extent of the disease, they are subdivided into pT4a and pT4b. Tumors that directly penetrate the peritoneal surface are classified as pT4a and tumors that are adherent to or directly invade other organs are assigned to the pT4b category.

Lymph node metastasis has been classified as N1 when 1–3 regional lymph nodes are involved by metastatic carcinoma and N2 with 4 or more lymph nodes involved. These two groups have been subdivided into pN1a (1 lymph node involved by metastatic carcinoma) and pN1b (metastasis in 2–3 lymph nodes), pN2a (metastasis in 4–6 lymph nodes), and pN2b (metastasis in 7 or more lymph nodes). These categories have been generated based on the different outcomes within these groups. Tumor deposits or satellite nodules are defined as discrete foci of tumor found in the pericolonic or perirectal fat away from the edge of the tumor with no evidence of residual lymph node tissue. Tumor deposit could be a result of discontinuous spread, venous invasion with extravascular spread, or a totally replaced lymph node.

Metastasis to 1 site, such as only the liver or lung or nonregional lymph nodes, is classified as M1a. Metastases to multiple sites or peritoneal surfaces are recorded as M1b. The absence of metastases or M0 can only be made at autopsy and would be annotated as aM0. If the tumor recurs, the "r" prefix is used for cancer staging (rTNM).

Tumor regression response is the pathological response to perioperative therapy and has a prognostic value. Chemoradiation in rectal cancer leading to complete eradication of tumor determined by pathological evaluation seems to portend a better prognosis than no response or incomplete response. Thus, the specimens from these patients should be thoroughly examined at the primary site, in the regional lymph nodes and for peritumoral satellite nodules or tumor deposits. The degree of response should be recorded and correlated with the prognosis. A 4-point grading system is used to evaluate the tumor regression response. No viable tumor is characterized as complete response (Grade 0), Single cell or small groups of cells is moderate response (Grade 1), residual cancer outgrown by fibrosis is minimal response (Grade 2), and minimal or no tumor kill is poor response (Grade 3).

Circumferential resection margin (CRM) involvement is another prognostic factor that is clinically important. This margin corresponds to any aspect of the colon or rectum that is uncovered by serosal layer and it needs to be dissected from the retroperitoneum or subperitoneum. In the rectum, the peritonalized surface and the nonperitonalized surface can be difficult to identify during the pathological examination of the resected specimen. Thus, surgeons are encouraged to mark the retroperitoneal reflection and the area of the deepest tumor penetration by a suture or a clip. The distance between the closest leading edge of the tumor and the CRM is another prognostic factor. Surgical clearance of 1 mm or less has been associated with local recurrence and should be recorded as a positive margin in rectal samples.

Residual tumor (R) refers to the completeness of the resection and is based on the status of the CRM and also includes any disease observed but not removed during the operation. Complete resection (R0) is designated as a complete resection with all margins uninvolved. Incomplete resection, or R1, refers to the presence of microscopic involvement of the surgical resection margins. Incomplete tumor resection with grossly visible tumor at the resection margin or regional lymph node involvement or incomplete primary tumor resection is characterized as R2.

As medicine advances, it has been feasible to identify isolated tumor cells (ITCs) and molecular node involvement. ITC is defined as a single malignant cell or a few tumor cells in microclusters. These cells usually can be either identified by hematoxylin and eosin (H & E) or the use of immunohistochemistry or molecular testing. Currently, the presence of ITC in regional lymph node is classified as pN0 and its prognostic significance remains unclear.

Some of the other independent prognostic factors include residual disease, histological type, histological grade, serum carcinoembryonic antigen and cytokine level, extramural venous invasion, and vascular invasion by carcinomas. Undifferentiated carcinoma, small cell carcinoma and signet ring cell carcinoma or poorly differentiated carcinoma have less a favorable outcome than other types of carcinoma. However, medullary carcinoma has a more favorable outcome. Submucosal vascular invasion by carcinomas arising in an adenoma is associated with higher risk of lymph node metastasis. Perineural invasion, lymphatic and vascular invasion are also associated with a less favorable outcome.

Another prognostic factor is the presence of a mutation in either codon 12 or 13 of *KRAS* and is associated with lack of response to treatment to anti-EGFR antibodies in patients

with metastatic colorectal carcinoma. Currently, molecular studies are not part of the staging system. However, in the future, evaluation of specific molecular factors might be a component of staging. Moreover, other factors such as age, gender, race, or ethnicity are also important as they may affect the disease outcome and response to therapy.

Colorectal Neuroendocrine Tumor Staging

Well-differentiated neuroendocrine (carcinoid) tumors of the colorectal region are classified according to the neuroendocrine tumors of the GI tract. These tumors in the colorectal region are rare. In the colon, the cecum is the most common location and some might originate from the appendix. Most of the carcinoids arising in the colon are more than 2 cm at the time of the diagnosis and involve the muscularis propria with the overall survival of 33–42%. Rectal carcinoids, on the other hand, have a more favorable outcome with low risk of metastasis. The overall survival for the rectal neuroendocrine tumors is 88.3%. Features predictive of poor outcome are tumor size greater than 2 cm and invasion of the muscularis propria. Neuroendocrine tumor invading lamina propria with the size of 2 cm or less is classified as T1. Tumors less than 1 cm and tumors between 1 cm and 2 cm are further subclassified as T1a and T1b, respectively. Neuroendocrine tumors with invasion of the muscularis propria or size greater than 2 cm with invasion of lamina propria or submucosa are assigned as T2. Stage T3 represents tumors invading through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissue. Tumors invading peritoneum or other organs are pathological stage T4.

References

1. Spring KJ, Zhao ZZ, Karamatic R, Walsh MD, Whitehall VL, Pike T, et al. High prevalence of sessile serrated adenomas with braf mutations: a prospective study of patients undergoing colonoscopy. Gastroenterology. 2006;131(5):1400–7.
2. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell. 1996;87(2):159–70.
3. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology. 1985;89(2):328–36.
4. Yachida S, Mudali S, Martin SA, Montgomery EA, Iacobuzio-Donahue CA. Beta-catenin nuclear labeling is a common feature of sessile serrated adenomas and correlates with early neoplastic progression after braf activation. Am J Surg Pathol. 2009;33(12):1823–32.
5. Yantiss RK, Oh KY, Chen YT, Redston M, Odze RD. Filiform serrated adenomas: a clinicopathologic and immunophenotypic study of 18 cases. Am J Surg Pathol. 2007;31(8):1238–45.
6. Cooper HS. Pathologic issues in the treatment of endoscopically removed malignant colorectal polyps. J Natl Compr Cancer Netw. 2007;5(9):991–6.
7. Parian A, Koh J, Limketkai BN, Eluri S, Rubin DT, Brant SR, et al. Association between serrated epithelial changes and colorectal dysplasia in inflammatory bowel disease. Gastrointest Endosc. 2016;84(1):87–95.
8. Jenkins MA, Hayashi S, O'Shea AM, Burgart LJ, Smyrk TC, Shimizu D, et al. Pathology features in Bethesda guidelines predict colorectal cancer microsatellite instability: a population-based study. Gastroenterology. 2007;133(1):48–56.
9. Wood LD, Salaria SN, Cruise MW, Giardiello FM, Montgomery EA. Upper gi tract lesions in familial adenomatous polyposis (fap): enrichment of pyloric gland adenomas and other gastric and duodenal neoplasms. Am J Surg Pathol. 2014;38(3):389–93.
10. Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in madh4 (smad4). Lancet. 2004;363(9412):852–9.
11. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in peutz-jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010;105(6):1258–64; author reply 1265.
12. Aretz S, Stienen D, Uhlhaas S, Loff S, Back W, Pagenstecher C, et al. High proportion of large genomic stk11 deletions in peutz-jeghers syndrome. Hum Mutat. 2005;26(6):513–9.
13. Volikos E, Robinson J, Aittomaki K, Mecklin JP, Jarvinen H, Westerman AM, et al. Lkb1 exonic and whole gene deletions are a common cause of peutz-jeghers syndrome. J Med Genet. 2006;43(5):e18.
14. Hizawa K, Iida M, Matsumoto T, Kohrogi N, Yao T, Fujishima M. Neoplastic transformation arising in peutz-jeghers polyposis. Dis Colon Rectum. 1993;36(10):953–7.
15. Cronkhite LW Jr, Canada WJ. Generalized gastrointestinal polyposis; an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. N Engl J Med. 1955;252(24):1011–5.
16. Slavik T, Montgomery EA. Cronkhite-Canada syndrome six decades on: the many faces of an enigmatic disease. J Clin Pathol. 2014;67(10):891–7.
17. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934–59.
18. Saha S, Hoda S, Godfrey R, Sutherland C, Raybon K. Carcinoid tumors of the gastrointestinal tract: a 44-year experience. South Med J. 1989;82(12):1501–5.
19. Anthony LB, Strosberg JR, Klimstra DS, Maples WJ, O'Dorisio TM, Warner RR, et al. The nanets consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. Pancreas. 2010;39(6):767–74.
20. Shia J, Tang LH, Weiser MR, Brenner B, Adsay NV, Stelow EB, et al. Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? Am J Surg Pathol. 2008;32(5):719–31.
21. Cuffy M, Abir F, Longo WE. Management of less common tumors of the colon, rectum, and anus. Clin Colorectal Cancer. 2006;5(5):327–37.
22. Meijer S, Peretz T, Gaynor JJ, Tan C, Hajdu SI, Brennan MF. Primary colorectal sarcoma. A retrospective review and prognostic factor study of 50 consecutive patients. Arch Surg. 1990;125(9):1163–8.
23. Friedman SL. Gastrointestinal and hepatobiliary neoplasms in aids. Gastroenterol Clin N Am. 1988;17(3):465–86.
24. Bonser RS, McMaster P, Acland PR, Parratt J. Fibrosarcoma of the transverse colon. J Surg Oncol. 1986;31(1):34–5.
25. Taxy JB, Battifora H. Angiosarcoma of the gastrointestinal tract. A report of three cases. Cancer. 1988;62(1):210–6.
26. Nahal A, Meterissian S. Lipoleiomyosarcoma of the rectosigmoid colon: a unique site for a rare variant of liposarcoma. Am J Clin Oncol. 2009;32(4):353–5.
27. Khalifa AA, Bong WL, Rao VK, Williams MJ. Leiomyosarcoma of the rectum. Report of a case and review of the literature. Dis Colon Rectum. 1986;29(6):427–32.

28. Posen JA, Bar-Maor JA. Leiomyosarcoma of the colon in an infant. A case report and review of the literature. Cancer. 1983;52(8):1458–61.
29. Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. Am J Surg Pathol. 2001;25(9):1121–33.
30. Lorenz HP, Wilson W, Leigh B, Schecter WP. Kaposi's sarcoma of the rectum in patients with the acquired immunodeficiency syndrome. Am J Surg. 1990;160(6):681–2; discussion 682–683.
31. Wong MT, Eu KW. Primary colorectal lymphomas. Color Dis. 2006;8(7):586–91.
32. Bairey O, Benjamini O, Blickstein D, Elis A, Ruchlemer R. Non-hodgkin's lymphoma in patients 80 years of age or older. Ann Oncol. 2006;17(6):928–34.
33. Myung SJ, Joo KR, Yang SK, Jung HY, Chang HS, Lee HJ, et al. Clinicopathologic features of ileocolonic malignant lymphoma: analysis according to colonoscopic classification. Gastrointest Endosc. 2003;57(3):343–7.
34. LeBrun DP, Kamel OW, Cleary ML, Dorfman RF, Warnke RA. Follicular lymphomas of the gastrointestinal tract. Pathologic features in 31 cases and bcl-2 oncogenic protein expression. Am J Pathol. 1992;140(6):1327–35.
35. Kodama T, Ohshima K, Nomura K, Taniwaki M, Nakamura N, Nakamura S, et al. Lymphomatous polyposis of the gastrointestinal tract, including mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma. Histopathology. 2005;47(5):467–78.
36. Yatabe Y, Nakamura S, Nakamura T, Seto M, Ogura M, Kimura M, et al. Multiple polypoid lesions of primary mucosa-associated lymphoid-tissue lymphoma of colon. Histopathology. 1998;32(2):116–25.
37. Varadarajulu S, Lewin D. Enteropathy-associated t-cell lymphoma involving the colon and extraintestinal b-cell lymphoma in celiac disease. Dig Dis Sci. 2003;48(7):1298–302.
38. Okada M, Maeda K, Suzumiya J, Hagimoto T, Wakamatsu S, Ohshima K, et al. Primary colorectal t-cell lymphoma. J Gastroenterol. 2003;38(4):376–84.
39. Ogawa A, Fukushima N, Satoh T, Kishikawa M, Miyazaki K, Tokunaga O. Primary intestinal t-cell lymphoma resembling lymphomatous polyposis: report of a case. Virchows Arch. 2000;437(4):450–3.
40. Williams G, Foyle A, White D, Greer W, Burrell S, Couban S. Intravascular t-cell lymphoma with bowel involvement: case report and literature review. Am J Hematol. 2005;78(3):207–11.
41. Wang HY, Fuda FS, Chen W, Karandikar NJ. Notch1 in primary effusion lymphoma: a clinicopathological study. Mod Pathol. 2010;23(6):773–80.
42. Edge SB, American Joint Committee on Cancer, American Cancer Society. Ajcc cancer staging handbook: from the ajcc cancer staging manual. 7th ed. New York: Springer; 2010.

Esophageal and Gastroesophageal Junction Tumors

4

Ebru Cilbir and Suayib Yalcin

Introduction

Esophageal cancer is a devastating disease with low survival rates. The management of locoregional disease has evolved over the past decade. Optimal staging and optimal treatment decisions according to stage, histologic type, and the location of disease are very important. A multidisciplinary approach to the patient is the major contributor to success. Surgery alone can be primarily for early-stage disease. Radiotherapy (RT) is an integral part of management of esophageal cancer. Preoperative chemoradiotherapy (CRT) is mostly used in standard care of stages II and III patients. Definitive CRT is mainly reserved for unresectable disease. Histology of the tumor and stage are the most important parameters for treatment decision making. Advanced and metastatic disease is managed mostly in a palliative manner, but chemotherapy can prolong survival. Emerging targeted and immunotherapy approaches are vulnerable.

Epidemiology

Esophageal cancer is the eighth most common cancer worldwide (6th in men and 13th in women) and the sixth most common cause of death from cancer. Around 80% of the cases occur in less-developed regions of the world. The incidence is highest in eastern Asia and more common in men than in women (male/female ratio 2:4). Mortality closely follows geographic distribution of the incidence [1]. It is a terrifying disease, mostly presenting with obstructing dysphagia in the locally advanced stage, and has a very poor prognosis. The majority of cancers of the esophagus are squamous cell carcinomas (SCCs) and adenocarcinomas (ACs). Also sarcomas, gastrointestinal stromal tumors (GISTs), and small-cell cancers can arise from the esophagus. The most important etiologic factors for SCCs are smoking and alcohol consumption, whereas the most common predisposing factor for AC is gastroesophageal reflux disease (GERD). The incidence of these major histologic types differs greatly geographically. The global incidence rates of SCC and AC were estimated to be 5.2 and 0.7 per 100,000, respectively, in 2012 [2]. SCCs were most common in Southern-Eastern and Central Asia, while ACs were most common in Northern-Western Europe, Northern America, and Oceania. Men had a substantially higher incidence than women, especially in the case of AC (male-to-female ratio AC 4:4; SCC 2:7) [2]. The incidence of esophageal AC (EAC) has increased greatly in the last 40 years in the Western world but is probably reaching a plateau [3, 4]. The most important suggestion for the cause of this increase is the concurrent epidemic of obesity, probably causing an increase in GERD and Barrett's esophagus [5]. According to anatomic location, data have implied that ACs of the lower esophagus and cardia of the stomach are the same disease. So esophagogastric junction (EGJ) tumors have merged as a distinct subsite, to facilitate surveillance, management, and research [6].

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database, the stage at diagnosis is distributed as follows: 20% localized, 31% regional, 38% distant, and 11% unknown. The 5-year estimated survival rates according to stages are as follows: 41.3% for localized disease, 22.8% for regional disease, and only 4.5% for distant metastatic disease [7].

Etiologic Factors

As mentioned earlier, the most important risk factors for esophageal SCCs are smoking and alcohol consumption. These two factors are also multiplicative of each other; that

E. Cilbir
Department of Medical Oncology, Dışkapı Yıldırım Beyazıt Education and Research Hospital, Ankara, Turkey

S. Yalcin (✉)
Department of Internal Medicine, Division of Medical Oncology, Hacettepe University School of Medicine, Institute of Cancer, Altındağ, Ankara, Turkey
e-mail: syalcin@hacettepe.edu.tr

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_4

means they synergistically increase the risk. Tobacco smoke contains polycyclic aromatic hydrocarbons, nitrosamines, and many other carcinogens such as pro-oxidative substances and reactive oxygen species [8]. Dietary factors such as low intake of fruits and vegetables, insufficiency of micronutrients (low intake of zinc, selenium, and folate), dietary carcinogens, and extremely high salt intake are also important risks. Chewing areca nuts and betel leaves in some regions of Asia [9], thermal irritation from consumption of hot food and drinks [10], and human papillomavirus (HPV) infection are also accused for esophageal SCC [11], but the results of studies are inconclusive. Some diseases or conditions associated with high risk are achalasia, caustic strictures, atrophic gastritis, prior gastrectomy history, and tylosis [12]. There had been concerns that bisphosphonates might be associated with an increase in esophageal cancer, but large meta-analyses have not identified any compelling evidence for a significantly raised risk of esophageal cancer for the prescribed bisphosphonates [13].

For EAC, the most important risk factor is GERD. EACs mostly arise on Barrett's metaplasia, so endoscopic screening is crucial in patients with Barrett's esophagus [14]. Smoking increases the risk of EAC also, especially in patients with Barrett's esophagus [15]. Obesity increases the risk of GERD, and through this association, it increases the risk of Barrett's esophagus and EAC [16]. But it is also suggested that obesity appears to be a risk factor of Barrett's esophagus and EAC independent of GERD [17]. The role of *Helicobacter pylori* infection for EAC is very contradictory. As shown in some studies, colonization by *H. pylori* in areas of gastric metaplasia [18, 19] could cause one to think there is an association between *H. pylori* and EAC like that seen in tumors of cardia of the stomach. But a meta-analysis has shown that there was an inverse relationship between *H. pylori* infection and EAC [20].

Clinical Manifestations

Early-stage disease is mostly asymptomatic, or in case of ACs related with chronic GERD disease. Early symptoms may be nonspecific. There may be transient sticking sensation, burning sensation, or retrosternal discomfort. Iron deficiency anemia may be seen due to chronic blood loss. In locally advanced disease, progressive solid food dysphagia develops and weight loss is seen because of dysphagia and also tumor-associated anorexia. Hoarseness may occur due to recurrent laryngeal nerve invasion. Tracheobronchial fistulas may be seen and cause coughing and recurrent pneumonias.

Diagnosis and Staging

Diagnosis is made by endoscopic evaluation. Endoscopy is an important tool in diagnosis and staging. After the confirmation of diagnosis with upper gastrointestinal endoscopy and biopsy, a thoracoabdominal computed tomography (CT) scan is done. If no distant metastasis is shown on CT, a positron emission tomography-CT (PET-CT) is indicated. If no evidence of metastatic disease is found, endoscopic ultrasound (EUS) should be done to evaluate local disease. For tumors at or above the carina, a bronchoscopy should be done to exclude tracheal invasion. If an early-stage cancer is suspected, endoscopic resection (ER) is important for accurate staging.

EGJ tumors are defined and described as tumors that have their center within 5 cm proximal and distal of the anatomical cardia. They are differentiated as the following three distinct tumor entities within this area:

- *Siewert Type I Tumor*: AC of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus (i.e., Barrett's esophagus) and which may infiltrate the EGJ from above.
- *Siewert Type II Tumor*: True carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the EGJ; this entity is also often referred to as "junctional carcinoma."
- *Siewert Type III Tumor*: Subcardial gastric carcinoma, which infiltrates the EGJ and distal esophagus from below [21].

The 2017 tumor-node-metastasis (TNM) staging for cancer of the esophagus and EGJ is derived from a machine-learning analysis of data from six continents from the Worldwide Esophageal Cancer Collaboration (WECC) [22–25].

EGJ staging has been limited by reliance on simple measurements to determine whether an AC is esophageal or gastric. The EGJ was redefined: ACs with epicenters no more than 2 cm into the gastric cardia are staged as esophageal ACs, and those extending further are staged as stomach cancers [22].

The American Joint Committee on Cancer (AJCC) TNM staging, according to the *AJCC Cancer Staging Manual, eighth edition* (2017), presents separate classifications for clinical (cTNM), pathological (pTNM), and postneoadjuvant (ypTNM) stage groups. It has separate clinical and pathological groupings for AC and SCC, but postneoadjuvant groupings are the same for both histologic types [26]. When accuracy of grade on biopsy is concerned, it is eliminated from clinical staging in the eighth edition. Assessment of cancer location (cL) is made during esophagoscopy. Cancer location is defined as the position of epicenter of the cancer as referenced to distance from the incisors. Clinically, the epicenter is determined from upper and lower border measurements, which also provide cancer length. Alternatively, cL can be determined from CT of the chest [22]. Cancer grade (cG) is determined as low grade (G1), moderately differentiated (G2), and poor differentiation or signet-ring cell morphology (G3). Cancer staging categories are given in Table 4.1. Prognostic stage groups are listed in Table 4.2 [22, 26].

Table 4.1 AJCC cancer staging categories for the esophagus and esophagogastric junction

Definition of primary tumor (T)	
Squamous cell carcinoma and adenocarcinoma	
T category	T criteria
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria, muscularis mucosa
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway

Definition of regional lymph nodes (N)	
Squamous cell carcinoma and adenocarcinoma	
N category	N criteria
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes

Definition of distant metastasis (M)	
Squamous cell carcinoma and adenocarcinoma	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Definition of histologic grade (G)	
Squamous cell carcinoma and adenocarcinoma	
G	G definition
Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Definition of location (L)	
Squamous cell carcinoma Location plays a role in the stage grouping of esophageal squamous cancers	
Location category	Location criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual*, *Eighth Edition* (2017), published by Springer International Publishing

Note: Location is defined by the position of the epicenter of the tumor in the esophagus

Table 4.2 AJCC clinical stage groups (cTNM) for the esophagus and esophagogastric junction

Squamous cell carcinoma			
Clinical (cTNM)			
When cT is…	And cN is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0-1	M0	I
T2	N0-1	M0	II
T3	N0	M0	II
T3	N1	M0	III
T1-3	N2	M0	III
T4	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Squamous cell carcinoma					
Pathological (pTNM)					
When pT is…	And pN is…	And M is…	And G is…	And location is…	Then the stage group is…
Tis	N0	M0	N/A	Any	0
T1a	N0	M0	G1	Any	IA
T1a	N0	M0	G2-3	Any	IB
T1a	N0	M0	GX	Any	IA
T1b	N0	M0	G1-3	Any	IB
T1b	N0	M0	GX	Any	IB
T2	N0	M0	G1	Any	IB
T2	N0	M0	G2-3	Any	IIA
T2	N0	M0	GX	Any	IIA
T3	N0	M0	Any	Lower	IIA
T3	N0	M0	G1	Upper/ middle	IIA
T3	N0	M0	G2-3	Upper/ middle	IIB
T3	N0	M0	GX	Any	IIB
T3	N0	M0	Any	Location X	IIB
T1	N1	M0	Any	Any	IIB
T1	N2	M0	Any	Any	IIIA
T2	N1	M0	Any	Any	IIIA
T2	N2	M0	Any	Any	IIIB
T3	N1-2	M0	Any	Any	IIIB
T4a	N0-1	M0	Any	Any	IIIB
T4a	N2	M0	Any	Any	IVA
T4b	N0-2	M0	Any	Any	IVA
Any T	N3	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

Squamous cell carcinoma			
Postneoadjuvant therapy (ypTNM)			
When yPT is…	And ypN is…	And M is…	Then the stage group is…
T0-2	N0	M0	I
T3	N0	M0	II
T0-2	N1	M0	IIIA
T3	N1	M0	IIIB
T0-3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1-2	M0	IVA
T4a	NX	M0	IVA

(continued)

Table 4.2 (continued)

Squamous cell carcinoma			
Postneoadjuvant therapy (ypTNM)			
When yPT is…	And ypN is…	And M is…	Then the stage group is…
T4b	N0-2	M0	IVA

Adenocarcinoma			
Clinical (cTNM)			
When cT is…	And cN is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIA
T2	N0	M0	IIB
T2	N1	M0	III
T3	N0-1	M0	III
T4a	N0-1	M0	III
T1-4a	N2	M0	IVA
T4b	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Adenocarcinoma				
Pathological (pTNM)				
When pT is…	And pN is…	And M is…	And G is…	Then the stage group is…
Tis	N0	M0	N/A	0
T1a	N0	M0	G1	IA
T1a	N0	M0	GX	IA
T1a	N0	M0	G2	IB
T1b	N0	M0	G1-2	IB
T1b	N0	M0	GX	IB
T1	N0	M0	G3	IC
T2	N0	M0	G1-2	IC
T2	N0	M0	G3	IIA
T2	N0	M0	GX	IIA
T1	N1	M0	Any	IIB
T3	N0	M0	Any	IIB
T1	N2	M0	Any	IIIA
T2	N1	M0	Any	IIIA
T2	N2	M0	Any	IIIB
T3	N1-2	M0	Any	IIIB
T4a	N0-1	M0	Any	IIIB
T4a	N2	M0	Any	IVA

Adenocarcinoma			
Postneoadjuvant therapy (ypTNM)			
When yPT is…	And ypN is…	And M is…	Then the stage group is…
T0-2	N0	M0	I
T3	N0	M0	II
T0-2	N1	M0	IIIA
T3	N1	M0	IIIB
T0-3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1-2	M0	IVA
T4a	NX	M0	IVA
T4b	N0-2	M0	IVA

Table 4.2 (continued)

Adenocarcinoma			
Postneoadjuvant therapy (ypTNM)			
When yPT is…	And ypN is…	And M is…	Then the stage group is…
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual, Eighth Edition* (2017), published by Springer International Publishing

Management

The traditional treatment of patients with localized cancer of the esophagus was surgery and/or RT. The type of therapy depends on the location and histopathology of the primary tumor, tumor stage, resectability of the lesion, and operability of the patient. But the survival results were poor. Only selected patients with resected T1-2 N0 disease showed some better results in some institutions, though the postoperative mortality rates were high—approximately 10% [27]. So there had been some efforts to develop systemic treatment options to increase the effect of RT. A prospective randomized trial (RTOG 85-01) showed that adding chemotherapy concomitantly to RT showed increased survival results compared with RT alone. Cisplatin +4-day infusional 5-fluorouracil (5-FU) was used as concomitant chemotherapy regimen [28]. Then, with the advance of CT and magnetic resonance imaging (MRI) scans, emergence of fluorodeoxyglucose (FDG)-PET, and EUS, the disease could be better staged, and with the use of multimodal treatment options, neoadjuvant chemotherapy, or combined CRT followed by surgery, patients are handled better. Also there had been advances in surgical techniques, such as minimally invasive esophagectomy or hybrid techniques with open surgery, to decrease postoperative mortality and morbidity. Moreover in early stages where involvement of regional lymph nodes is expected to be minimal, endoscopic mucosal resection (EMR) can optimally stage and also treat the disease without need for radical surgery. Treatment decisions of these patients should be discussed by multidisciplinary tumor boards.

Although EGJ ACs are also included in studies of gastric cancer, upfront surgery plus adjuvant chemotherapy ± CRT or perioperative chemotherapy may be options according to stage of disease.

We categorize disease without any distant metastasis as early disease (Tis, T1a/b, and N0-1) and locally advanced disease (T2-4a, N1-3) for optimum treatment decision.

Management of Early Disease

Esophagectomy is the main curative therapy for T1 N0 early esophageal cancer [29]. EMR and/or ablation therapy—radiofrequency ablation (RFA), cryoablation, photodynamic therapy—may be options and give equal cure rates as esophagectomy in specialized centers for Tis and T1a tumors [30–32].

Endoscopic Therapy

Several cohort studies suggest the use of EMR or endoscopic submucosal dissection (ESD) for T1a tumors confined to superficial mucosa [30, 33–35]. In some other studies, muscularis mucosa and even upper third submucosal involvement is also included [35, 36].

One of these studies included a total of 349 patients with Barrett's esophagus and high-grade dysplasia (61 patients) or early AC (288 patients) treated with ER and/or ablation therapy. At a median follow-up of 63.6 months, complete response (CR) was observed in 96.6% of the patients. Surgery was necessary in only a few of the patients (3.7%) when endoscopic therapy failed. Metachronous lesions developed during the follow-up in 21.5% of the patients. The risk factors most frequently associated with recurrence were piecemeal resection, long-segment Barrett's esophagus, no ablative therapy of Barrett's esophagus after CR, time until CR achieved >10 months, and multifocal neoplasia. No patient died of esophageal cancer [30].

The concerns that should be measured before deciding whether to do ER or radical surgery are as follows: the possibility of lymph node metastases, completeness of endoscopic resectability, early and late complications, local recurrence, and development of a metachronous cancer [35].

Lymph node status is the most important prognostic factor. EUS has better diagnostic performance than CT and PET-CT, but the problem of finding the ideal method for detecting lymph node metastases is not solved yet. One important issue is the fact that a significant number of patients are restaged with the endoscopic procedure, different from the EUS staging done prior to the procedure. So in selected patients, it would be ideal if ER could be a part of the pretreatment diagnostics [35]. And also it provides more histologic data than the depth of the tumor, like grade, lymphovascular invasion, microvascular invasion, piecemeal resection, and accompanying carcinoma in situ component, which would provide more prognostic information before giving the treatment decision.

In a meta-analysis of 21 studies with ESD for superficial esophageal carcinoma, 1152 patients and 1240 lesions were included. The pooled en block resection rate was 99%, and R0 resection rate was 90%. The most common complication was stenosis with a pooled rate of 5%. The incidence of postoperative stenosis decreased significantly after 2011 (2%) compared with that before 2011 (9%). Perforation was reported in 1% [37].

In a systemic review, including studies of endoscopic or surgical resection of T1a/T1b tumors, the effects of outcomes of 4241 patients enrolled in 80 retrospective studies were investigated. There were no significant differences between EMR and ESD concerning procedural complications, number of patients submitted to surgery, positive specimen margins, lymph node positivity, local recurrence rates, and metachronous cancer development. In instances of a predicted piecemeal tumor resection, ESD performed better since the number of cases was significantly less and local recurrence rates were, therefore, significantly lower. A higher rate of esophageal stenosis was observed following ESD. Local tumor recurrence after ER was best predicted by grade 3 differentiation, metachronous cancer development by the carcinoma in situ component, and lymph node positivity by lymphovascular invasion. According to this study, the authors commented that T1b esophageal cancer should be managed with surgical resection and systematic lymphadenectomy since even Sm1 (depth of invasion in submucosal layer: Sm1, invading more superficial layer; Sm2, invading middle third; Sm3, invading deeper submucosal layer) invasion was in the constructed model, while the histologic type and presence of specific predictors could likely alter the surgeon's policy and perspective of multimodality management. The best predictors of lymph node positivity in SCC were Sm3 invasion and microvascular invasion. For AC, the most important predictor was lymphovascular invasion [35].

A retrospective study from a single institution from Japan compared the results of endoscopic therapy for early esophageal cancer in respect to SCC and AC; 230 patients were included. Although most of the patients had SCC (204 SCC, 26 AC patients), long-term results showed that the rate of recurrence, mostly metachronous, was more in SCC than in AC. The authors concluded that more rigorous endoscopic follow-up is needed after ER in patients with SCC than those with AC [38].

The goal of endoscopic therapy should be complete removal of early-stage disease: pTis, pT1a, selected superficial T1b lesions without lymphovascular invasion (LVI), and preneoplastic lesions (Barrett's esophagus). ER is successful when negative deep and lateral margins are achieved [39]. Endoscopic therapies should be performed in specialized centers.

The studies comparing ER with surgery are limited; there exist only a few retrospective comparisons. Long-term outcomes are similar, with higher recurrence rates with endoscopic therapy requiring recurrent therapy in the follow-up but with fewer complications [40, 41].

The first population-based data to support the effectiveness of endoscopic therapy for superficial esophageal cancer came from analysis of the population-based National Cancer

Institute Surveillance, Epidemiology, and End Results (SEER) registry. In this analysis, 742 patients with Tis and T1 esophageal cancer were included; 13.3% of the patients were treated endoscopically, and the remainder were treated with surgery. The relative hazard for esophageal cancer-specific mortality in the endoscopically treated group was not different from that of the surgery group [42].

As a conclusion, Tis and T1a of SCCs and ACs are effectively treated with endoscopic therapy especially when they are small (≤2 cm). In ACs, endoscopic therapy for superficial T1b lesions can be an option. ER permits good histologic determination of the specimen, so it is preferred over ablation. Poor differentiation and LVI should be exclusions for endoscopic therapies because of high risk of relapse unless the patient is a poor candidate for esophagectomy [30, 39, 43, 44]. When the lesion is larger, ablation can be an option because ER can result in more complications. But, areas of nodularity and ulceration should be resected rather than ablated. There are more data for ablative techniques for ACs than SCCs. Pretreatment staging with EUS and also with ER should be well evaluated before choosing any ablative therapy. After endoscopic therapy of the early-stage disease, ablative therapy of the residual Barrett's esophagus should be done [39, 45–47].

Esophagectomy

Esophagectomy may be the initial treatment approach for T1-2 N0 esophageal cancer, but, as discussed previously, endoscopic treatment may be preferred over surgery in selected T1a tumors. Also it is controversial whether to operate T2 N0 tumors directly or classify these tumors among locally advanced disease and give preoperative treatment. As will be mentioned in the following section, T2 N0 tumors are included in 3 positive trials evaluating preoperative CRT, but the actual representation of this subgroup is only known in the Cancer and Leukemia Group B (CALGB) 9781 study and in only 3 of the 56 patients [48–50]. So these studies cannot be conclusive with this subgroup of patients. The French Francophone de Cancérologie Digestive (FFCD) 9901 trial involved stage I or II patients, 19% of which are stage I. This study did not show a benefit of preoperative CRT, but it may be underpowered to show an overall survival (OS) benefit [51, 52].

For more advanced stages, esophagectomy is done after neoadjuvant chemotherapy or CRT for resectable tumors and patients fit for a major surgery. These are Tany N1, T3 N0, and selected T4 disease with invasion of local structures that can be resected en block; that is, pericardium, pleura, and diaphragm. After neoadjuvant treatment, patients are restaged and the ones who remain resectable are referred to surgery.

For locally advanced unresectable tumors, salvage surgery can still be an option after definitive CRT. Presence of metastatic disease defers patients from radical surgery.

Patients with either SCC or AC involving the middle or lower third of the esophagus, with the exception of EGJ tumors, generally require a total esophagectomy and extensive lymph node sampling because of the risk of skip lesions in submucosa and skipping micrometastases in lymph nodes [53–55]. In the setting of Barrett's disease, early ACs located distally may be less radically resected through transhiatal resection [56]. The choice of technically different procedures, such as transthoracic (Ivor-Lewis), transhiatal, tri-incisional esophagectomy, and the extent of lymph node dissection, may be different according to tumor location, extension, adherence to surrounding structures, the conduit to be used for gastrointestinal continuity, and the preference of the surgeon. Gastric interposition, jejunal, or colonic segments may be used as a conduit for gastrointestinal continuity.

Whatever the approach is, surgical management of tumors in the intra-abdominal part of esophagus or EGJ tumors should result in R0 resection with 4-cm gastric margin and 5-cm esophageal margin and resection of at least 15 nodes in basins appropriate for tumor location [57, 58].

For cervical esophageal cancer, definitive CRT is mostly preferred over surgery. But for patients who failed CRT, a sophisticated surgical resection with removal of portions of pharynx, larynx, thyroid gland, and proximal esophagus may be needed with attention to unilateral or bilateral neck lymph node dissections [59].

Advances in surgical techniques such as minimally invasive esophagectomy or hybrid techniques with open surgery have decreased postoperative mortality and morbidity.

Adjuvant Treatment

Patients with completely resected T4 or node-positive tumors who have not received neoadjuvant therapy have poor prognosis.

For patients with AC of EGJ, as they are included in gastric cancer trials, adjuvant chemotherapy and CRT are indicated according to the results of the Intergroup Trial [60]. For other patients, there are no randomized trials showing benefit of adjuvant treatment.

Some retrospective reports and phase II trials show potential benefit of adjuvant therapy, but others do not, for parts of esophageal cancer other than EGJ tumors [61–66]. The need for extra treatment in operated node positive or T4 tumors that did or did not have neoadjuvant treatment is obvious, but the benefit is uncertain based on available data.

In a Japanese trial of stage II or III patients with esophageal SCC, preoperative versus postoperative chemotherapy was compared. Patients received two cycles of cisplatin and fluorouracil prior to or after surgery. Five-year OS was significantly higher in the group receiving preoperative chemotherapy [67].

As most data show a benefit from preoperative chemotherapy or CRT, preoperative treatment is generally recom-

mended from stage T2 N0 and TanyN1 esophageal cancer of either histology.

Management of Locally Advanced Disease

This is a heterogeneous group of patients: T2-4N0 or TanyN1-3. Surgery was considered to offer the best chance of prolonged survival, but 50–60% of patients are not suitable for operation due to either tumor extent or medical comorbidity [68, 69]. Operable patients should be medically fit and should have a resectable tumor. Even in this group, high-risk patients do worse after radical surgery. Data from the Worldwide Esophageal Cancer Collaboration of 4627 patients treated with esophagectomy alone showed that the 5-year survival rate was 42% for all stages and 15% for node-positive patients [70]. Given this low survival and high postoperative complications and morbidity, RT became a noninvasive option, but again with unsatisfactory outcomes [71]. Better outcomes were observed with combined chemotherapy and RT.

Definitive Chemoradiotherapy

In the Radiation Therapy Oncology Group (RTOG) 85-01 trial, Herskovic et al. showed that concurrent therapy with cisplatin and fluorouracil and radiation is superior to radiation alone for patients with localized carcinoma of the esophagus. In this study, patients had locoregional disease at thoracic esophagus and most were SCC. Patients received 64 Gy in the RT-alone arm and 50-Gy RT with concurrent administration of two cycles of infusional 5-FU 1000 mg/m^2 days 1–4 plus cisplatin 75 mg/m^2 on day 1 of weeks 1 and 5, with two additional chemotherapy cycles 3 weeks apart, after completion of RT on the concurrent arm. The median OS was 8.9 months in the RT-alone arm, as compared with 12.5 months in the patients treated with CRT. In the former group, the survival rates at 12 and 24 months were 33% and 10%, respectively, whereas they were 50% and 38% in the patients receiving combined therapy ($P < 0.001$). In the randomized part of the trial, at 5 years of follow-up, the OS for combined therapy was 26% compared with 0% following RT. In the succeeding nonrandomized part, combined therapy produced a 5-year OS of 14%. Persistence of disease despite therapy was the most common mode of treatment failure [28, 72].

In the INT 0123 (RTOG 94-05) study, the concurrent regimen (same regimen with RTOG 85-01), when compared with standard dose RT (50.4 Gy) and high-dose RT (64.8 Gy), the higher dose did not increase survival or locoregional control. High-dose RT was more toxic [73]. If a nonoperative approach is selected for locally advanced esophageal cancer, combined CRT but concomitant is better over RT alone. Sequential chemotherapy and RT approaches have increased toxicity with no benefit on survival [74].

Different chemotherapy regimens other than cisplatin and fluorouracil have also shown activity in concomitant use with definitive RT, such as FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or paclitaxel and carboplatin [75, 76]. In the PRODIGE5/ACCORD17 trial, definitive CRT with six cycles of FOLFOX (three of which were given concomitantly; oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2, bolus fluorouracil 400 mg/m^2, and infusional fluorouracil 1600 mg/m^2 [FOLFOX] over 46 hours) was compared with standard four cycles of cisplatin–fluorouracil (two of which were given concomitantly). With some different toxicity profiles, FOLFOX could be an alternative chemotherapy regimen used concomitantly with RT. Neurotoxicity was more frequent with FOLFOX, but nephrotoxicity and mucositis were less frequent than with cisplatin–fluorouracil [75]. In the other trial, weekly paclitaxel (50 mg/m^2) plus carboplatin (AUC = 2) was compared with the standard cisplatin–fluorouracil regimen given concomitantly with definitive RT. This study showed comparable outcome, in terms of disease-free survival (DFS) and OS for carboplatin–paclitaxel compared to cisplatin–fluorouracil, with lower toxicity rates and higher treatment compliance [76].

Neoadjuvant Treatment

Better survival was observed with preoperative concurrent CRT compared with surgery only and became a preferred approach for potentially resectable esophageal cancer. In a study comparing multimodal therapy to surgery alone in resectable esophageal AC, 58 patients were assigned to 40-Gy RT given concomitantly with two courses of cisplatin and fluorouracil chemotherapy followed by surgery, and 55 patients were assigned to the surgery-alone arm. Thirteen of the 52 patients (25%) who underwent surgery after multimodal therapy had complete remissions as determined pathologically. The median survival of patients assigned to multimodal therapy was 16 months, as compared with 11 months for those assigned to surgery alone ($P = 0.01$). At 1, 2, and 3 years, 52%, 37%, and 32% of patients, respectively, assigned to multimodal therapy were alive, as compared with 44%, 26%, and 6% of those assigned to surgery, with the survival advantage favoring multimodal therapy reaching significance at 3 years ($P = 0.01$) [48].

CALGB 9781 was designed to compare the advantage of trimodality therapy to esophagectomy alone for operable esophageal cancer. Due to poor accrual, only 56 patients were enrolled. The preoperative CRT (with cisplatin 100 mg/m^2 plus fluorouracil 1000 mg/m^2 for 4 days in weeks 1 and 5 concurrent with 50.4-Gy radiation therapy) plus surgery arm was compared with a surgery-only arm. Five-year survival was 39% vs 16% in favor of trimodality therapy. And the preoperative treatment did not increase perioperative morbidity and mortality. One important observation was the 40% rate of pathologic CR (pCR) in 25 assessable patients [49].

The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial—a Dutch study of patients with potentially resectable esophageal and EGJ cancer (clinical T1N1M0 or T2-3N0-1M0)—compared preoperative CRT (using weekly paclitaxel 50 mg/m^2 and carboplatin AUC = 2; radiation dose of 41.4 Gy over 5 weeks) with surgery alone. In this study, both SCC and AC were included, but the majority of the patients had AC and nearly 10% of patients had EGJ tumors. Of the patients in the CRT arm, 95% were able to complete the entire neoadjuvant CRT regimen. After a median follow-up for surviving patients of 84 months, median OS was 48.6 months in the neoadjuvant CRT plus surgery group and 24 months in the surgery-alone group (hazard ratio [HR] 0.68; P = 0.003). Median OS for patients with SCC was 81.6 months in the neoadjuvant CRT plus surgery group and 21 months in the surgery-alone group (HR 0.48; P = 0.008). For patients with ACs, median OS was 43.2 months in the neoadjuvant CRT plus surgery group and 27.1 months in the surgery-alone group (HR 0.73; P = 0.038). So this trial shows that neoadjuvant CRT before definitive surgery improves survival of resectable locally advanced esophageal (regardless of histology) and EGJ tumors [50, 77].

Another trial, the French FFCD 9901, rendered the effect of preoperative CRT for an earlier staged group of patients (stage I or II; T1N0/N+, T2N0/N+, or T3N0) with esophageal or EGJ tumors (70% of all population was SCC). The CRT protocol was 45 Gy in 25 fractions over 5 weeks with two courses of concomitant chemotherapy composed of fluorouracil 800 mg/m^2 and cisplatin 75 mg/m^2. Pretreatment disease was stage I in 19%, IIA in 53.3%, and IIB in 27.7% of patients. Compared with surgery alone, neoadjuvant CRT with cisplatin plus fluorouracil did not improve the R0 resection rate or survival, but did enhance postoperative mortality (postoperative mortality rate of 11.1% versus 3.4%; P = 0.049). There were no subgroups in favor of neoadjuvant CRT, such as node positivity or histology (SCC vs. AC) [51]. So this study could not show the advantage of preoperative CRT that was shown in the Dutch study. The authors concluded that neoadjuvant therapy does not improve survival and increases postoperative mortality in patients with early-stage disease [51].

Of course, there are some differences between two studies; the main ones being the stages and the histology of patients in these two studies. The French study included much earlier stages and 70% of patients had SCC, while the Dutch study involved more advanced local disease and predominantly ACs. However, patterns of failure analysis showed a significant improvement in local control in patients who received neoadjuvant therapy, nearly halving the rate of locoregional recurrence (29% vs. 15%). Disease recurrence rates were also significantly reduced in patients receiving neoadjuvant treatment. These local failure rates mirror the Dutch trial rates of locoregional recurrence reduction from 34% (surgery only) to 14% (neoadjuvant therapy and surgery) in a more advanced group of patients. These data highlight the challenge of surgery in extirpating all locoregional disease even in patients with early-stage disease [52]. So it can also be possible that the French study could be underpowered to show this local failure improvement with neoadjuvant CRT to translate to OS. Also, as postoperative mortality is significantly higher than surgery alone in the French trial in contrast to the Dutch trial, there may be effect of this early mortality on OS results. This can be due to different concomitant chemotherapy regimens and RT protocols used in these two trials [52].

In a meta-analysis of 12 randomized studies comparing preoperative CRT (either concurrent or sequential) versus surgery alone, including the aforementioned three studies (CALGB 9781, CROSS, and FFCD 9901), the hazard ratio for all-cause mortality for neoadjuvant CRT was 0.78 (P < 0.0001); the HR for SCC only was 0.80 (P = 0.004) and for AC only was 0.75 (P = 0.02). There was little association between the risk of postoperative mortality (both in-hospital and 30-day) and neoadjuvant interventions. This meta-analysis also included the studies comparing neoadjuvant chemotherapy versus surgery alone. The HR for all-cause mortality for neoadjuvant chemotherapy was 0.87 (P = 0.005); the HR for SCC only was 0.92 (P = 0.18) and for AC only was 0.83 (P = 0.01). Also two studies in this meta-analysis compared neoadjuvant CRT with neoadjuvant CT. The HR for overall indirect comparison of all-cause mortality for neoadjuvant CRT versus neoadjuvant chemotherapy was 0.88 (P = 0.07) [78].

A meta-analysis tried to clarify the benefits of neoadjuvant and definitive treatment of esophageal SCC. It included nine randomized controlled trials (RTCs) involving neoadjuvant CRT versus surgery, eight involving neoadjuvant chemotherapy versus surgery, and three involving neoadjuvant treatment followed by surgery or surgery alone versus definitive CRT. The likelihood of R0 resection was significantly higher after neoadjuvant treatment (for CRT, an HR of 1.15, P = 0.043, and for chemotherapy, an HR of 1.16, P = 0.006, were observed). But high levels of heterogeneity was noted. Morbidity rates were not increased after neoadjuvant CRT, but 30-day mortality was nonsignificantly higher with combined treatment compared with surgery alone. Morbidity and mortality after neoadjuvant chemotherapy did not differ from surgery alone. Survival after neoadjuvant CRT was higher compared to surgery alone. The HR of OS was 0.81 (P = 0.008) after neoadjuvant CRT. However, survival after neoadjuvant chemotherapy was not increased; the HR of OS was 0.93 (P = 0.368). In the third group of studies, definitive CRT versus neoadjuvant treatment followed by surgery or surgery alone was compared. None of the RCTs reporting outcome after definitive CRT demonstrated a significant survival benefit, but treatment-related mortality rates

were lower: HR 7.60 (P = 0.007). No morbidity difference was noted between treatment groups [79].

The studies show that response to preoperative therapy, particularly pCR, predicts a better DFS and OS [80–85]. In a review of 22 studies, the authors tried to quantify the survival benefit of pCR vs. residual disease at esophagectomy. The OS for patients with pCR was 93.1%, 75.0%, and 50.0% at 2, 3, and 5 years, respectively, whereas it was 36.8%, 29.0%, and 22.6% for patients with residual tumor (P < 0.025). Median survival times for patients with pCR were significantly longer than those for patients with residual tumor (P = 0.011). The patients with a pCR were 2.8-fold more likely to survive at 5 years. The absolute survival benefit of pCR was 33–36% [85].

So to increase the rate of pCR, researchers tried to intensify the preoperative treatment by adding induction chemotherapy before neoadjuvant CRT [86–89]. Indeed, there are no randomized trials to search the benefit of induction chemotherapy and neoadjuvant CRT over neoadjuvant CRT alone. But in one phase III trial, the Preoperative Chemotherapy or Radiochemotherapy in Esophago-gastric Adenocarcinoma Trial (POET), induction chemotherapy alone before surgery was compared with induction chemotherapy plus neoadjuvant CRT and surgery in patients with AC of the lower esophagus or gastric cardia. Although the study was closed prematurely, the pCR was higher in the CRT group and preoperative CRT improved the 3-year survival rate from 27.7% to 47.4% [90], P = 0.07 [90].

PET scan is thought to be a predictor of induction therapy response and could help to tailor therapy according to response. In phase II of the MUNICON trial, patients with locally advanced EGJ ACs were treated with 2 weeks of platinum and fluorouracil-based induction chemotherapy. Those with decreases in tumor glucose standard uptake values (SUVs), predefined as decreases of 35% or more at the end of the evaluation period and measured by PET, were defined as metabolic responders. Responders continued to receive neoadjuvant chemotherapy of folinic acid and fluorouracil plus cisplatin, or folinic acid and fluorouracil plus cisplatin and paclitaxel, or folinic acid and fluorouracil plus oxaliplatin for 12 weeks and then proceeded to surgery. Metabolic nonresponders discontinued chemotherapy after the 2-week evaluation period and proceeded to surgery. Early PET responders to CT had significantly better event-free survival compared with PET nonresponders (30 vs. 14 months). This study also suggested benefit of early identification of PET nonresponders who went to immediate surgical resection rather than completion of preoperative chemotherapy [91]. Afterward, the MUNICON II trial was conducted to evaluate whether salvage neoadjuvant CRT could increase R0 resection rates in the nonresponder group. The prognosis of nonresponders was poor and addition of CRT did not increase the R0 resection rate [92].

This PET-guided treatment algorithm was further investigated in a recent CALGB 80803 trial. In this trial, T2-4 or N+ surgically resectable esophageal and EGJ ACs were randomized to receive either three doses of an induction chemotherapy with modified FOLFOX6 or four times weekly carboplatin and paclitaxel. Patients were then evaluated with PET scan, and responders were defined as ≥35% decrease in SUV. PET responders continued the same regimen with concurrent RT (50.4 Gy). PET nonresponders crossed over to alternate chemotherapy (weekly carboplatin and paclitaxel for upfront FOLFOX receivers and vice versa) with concurrent RT of same dose. Surgical resection was planned 6 weeks after completion of CRT. This early response assessment and switching from ineffective therapy to alternate chemotherapy resulted in a pCR rate of 18% for PET nonresponders. FOLFOX induction and concurrent therapy in responders resulted in a very promising pCR rate of 38% [93].

Nonoperative Treatment

As pCR rates are higher in SCC following neoadjuvant CRT, if an endoscopic CR is achieved, we may assume that a nonoperative management could be an option following initial CRT. But data are lacking on nonsurgical follow-up of endoscopically complete responders after initial CRT.

There is a randomized study comparing induction chemotherapy plus CRT (RT of 65 Gy) alone with the same treatment regimen but 40-Gy RT given preoperatively followed by surgery in locally advanced esophageal SCC. OS was equivalent between the two treatment groups. Local progression-free survival (PFS) was better in the surgery group. Treatment-related mortality was significantly increased in the surgery group than in the CRT group (12.8% vs. 3.5%). Clinical tumor response to induction chemotherapy was the single, independent prognostic factor for OS. So adding surgery to CRT improved local tumor control but did not increase survival. Tumor response to induction chemotherapy identifies a favorable prognostic group within these high-risk patients, regardless of the treatment group [94]. Long-term results revealed OS rates at 3 years (31% vs. 24%), 5 years (28% vs. 17%), and 10 years (19% vs. 12%) in the surgery vs. definitive CRT groups [95].

Another study (FFCD 9102) comparing preoperative treatment plus surgery with nonsurgical treatment only included operable T3N0-1M0 thoracic esophageal cancer patients, of whom 88.8% had SCC and 11.2% had AC. Of the patients, 451 received induction CRT as two cycles of cisplatin–fluorouracil (days 1–5 and 22–26) and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1–5 and 22–26) concomitant RT. Patients with response and no contraindication for either therapy (n = 259) were randomized between surgery (arm A) and continuation of chemoradiation (arm B) (one cycle of cisplatin–fluorouracil and either conventional [20 Gy] or split-course [15 Gy] RT

and two additional chemotherapy cycles). The 2-year survival rate was 34% in arm A versus 40% in arm B (HR = 0.90; adjusted $P = 0.44$). The median survival time was 17.7 months in arm A compared with 19.3 months in arm B. The 2-year local control rate was 66.4% in arm A compared with 57.0% in arm B, and stents were less required in the surgery arm (5% in arm A vs. 32% in arm B; $P < 0.001$). The 3-month mortality rate was 9.3% in arm A, compared with 0.8% in arm B ($P = 0.002$). Cumulative hospital stay was 68 days in arm A compared with 52 days in arm B ($P = 0.02$). The assessment of longitudinal quality of life measures of this study showed that it is in favor of the CRT arm in the early period after treatment. But among 2-year survivors, there were no differences between both groups. These data suggest that, in patients with locally advanced thoracic esophageal cancers, especially SCC, who respond to CRT, there is no benefit for the addition of surgery after chemoradiation compared with the continuation of additional CRT [96, 97].

Of the 451 registered patients in the trial, 192 were not randomized. Among them, 111 were clinical nonresponders. Median OS was significantly shorter for nonrandomized patients (11.5 months) than for randomized patients (18.9 months; $P = 0.0024$). However, for the 112 nonrandomized patients who underwent surgery, median OS was not different from that in randomized patients: 17.3 versus 18.9 months ($P = 0.58$). Concerning clinical nonresponders, median OS was longer for those who underwent surgery compared to nonoperated patients—17.0 versus 5.5 months (HR = 0.39; $P < 0.0001$)—and again was not different from that in responding, randomized patients ($P = 0.40$). So in patients with locally advanced thoracic esophageal cancer, OS did not differ between responders to induction CRT and patients having surgery after clinical failure of CRT. Surgery should, therefore, be considered in those patients who are still operable [98].

A Cochrane analysis was made to compare surgery to nonsurgical management for operable EC. Eight trials, including the aforementioned two trials, of 1114 patients were included. The nonsurgical treatment was CRT in five trials and definitive RT in three trials. There was no difference in long-term mortality between CRT and surgery (HR 0.88). The long-term mortality was higher in RT than in surgery (HR 1.39). There was no difference in long-term recurrence between nonsurgical treatment and surgery (HR 0.96). The proportion of people with dysphagia at the last follow-up visit prior to death was higher with definitive CRT compared to surgical treatment (relative risk [RR] 1.48). According to this meta-analysis, CRT appears to be at least equivalent to surgery in terms of short-term and long-term survival in people with esophageal SCC who are fit for surgery and are responsive to induction CRT. However, there is uncertainty in the comparison of definitive CRT versus surgery for esophageal AC [99].

The data for nonsurgical management of esophageal AC are only limited to retrospective series [100, 101]. In a study of localized gastroesophageal cancer, mainly of ACs (92%), patients were treated with CRT rather than surgery. Of 284 patients, 218 (77%) achieved clinical CR (determined by endoscopic biopsies and a PET scan showing only physiological uptake). However, only 67 (31%) of the 218 achieved pCR. So the specificity of clinical CR for pCR is too low to be used for clinical decision making on delaying or avoiding surgery [102].

Another study evaluating post-CRT FDG-PET scan involved patients with histologically confirmed (75% AC) stage I to IVA esophageal cancer receiving CRT with or without resection with curative intent. PET-CR was defined as standardized uptake value (SUVmax) ≤ 3. PET-CR patients receiving definitive CRT had excellent outcomes (2-year OS, 71% vs. 11%, $P < 0$ 0.01; 2-year freedom from local failure, 75% vs. 28%, $P < 0.01$). On multivariate analysis of patients treated with CRT, PET-CR was the strongest independent prognostic variable. PET-CR predicted for improved outcomes regardless of histology, although patients with AC achieved a PET-CR less often. Definitive CRT patients achieving PET-CR had excellent outcomes equivalent to trimodality therapy despite poorer baseline characteristics. In contrast, those patients undergoing trimodality therapy ($n = 55$) showed no difference in outcome according to the post-CRT PET findings, probably because those patients who had residual disease underwent resection. The authors concluded that patients who achieve a PET-CR may not benefit from added resection given their excellent outcomes without resection. But these results should be evaluated with caution. Validation of these results in prospective trials of FDG-PET-directed therapy for esophageal cancer should be done [103]. A prospective study involving 60 patients with operable locally advanced esophageal cancer, receiving neoadjuvant CRT and surgery, failed to demonstrate an association between a pathological response (either complete or major) and the percentage change in pre- and post-CRT FDG-PET results. Also no significant association was found between metabolic imaging and recurrence or survival [104].

Can nonsurgical management with CRT alone be enough for operable esophageal cancer? This question is not solved precisely yet. For patients with SCCs who are endoscopically documented to have CR after definitive CRT, surveillance may be an option. But, higher locoregional failure is an important issue. So resection is a better choice for optimal surgical candidates. However, for ACs, as the rate of pCR is lower than for SCCs, and without enough evidence, nonsurgical treatment of ACs is not recommended.

Management of Potentially Resectable Esophagogastric Junction Adenocarcinomas

As mentioned earlier, EGJ ACs are also included in studies of gastric cancer, and upfront surgery plus adjuvant chemotherapy ± CRT or perioperative chemotherapy may be other options with preoperative chemoradiation according to stage of disease.

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study demonstrated the benefit of perioperative chemotherapy with epirubicin–cisplatin and infusional fluorouracil (ECF) versus surgery alone for resectable esophagogastric AC. In this study, 26% of the enrolled patients had AC of the distal esophagus and esophagogastric junction; the remaining having gastric AC. There was evidence of downstaging with preoperative chemotherapy and increase in survival in the perioperative chemotherapy arm [105]. The results of the French FNLCC and FFCD trial confirmed data in favor of perioperative chemotherapy with cisplatin and fluorouracil compared with surgery alone. In this study, 75% of patients had lower esophagus or esophagogastric junction tumors [106]. Based on these two studies, perioperative chemotherapy had become an acceptable standard of care of these patients. A phase III study of perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus ECF/ECX (capecitabine instead of fluorouracil) for resectable gastric or GEJ ACs (FLOT/AIO) showed an increase in the curative surgery rate, PFS, and OS with the FLOT regimen [107]. According to this study, the new standard of care, perioperative chemotherapy in this group of patients had been FLOT.

The aforementioned CROSS study also had 75% of enrolled patients being AC of the distal esophagus or GEJ, so preoperative CRT is also an option.

The question of best neoadjuvant/perioperative approach for AC of esophagogastric cancers is still unanswered. There are ongoing studies addressing this question, and results are awaited for the NEOadjuvant Trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study (Neo-AEGIS) (perioperative capecitabine and oxaliplatin); ESOPEC (perioperative FLOT regimen; four cycles pre, four cycles post); and TOPGEAR (three pre + three post cycles of ECF/ECX vs. induction two cycles of ECF then concomitant CRT with 5-FU and three cycles of same chemotherapy postoperative).

Management of Locally Advanced Disease: Unresectable and Inoperable

Unresectable disease is defined as T4b disease that includes invasion of the aorta, trachea, heart, great vessels, or presence of a tracheoesophageal fistula. T4a disease—which includes invasion of the pleura, pericardium, or diaphragm—is considered to be potentially a resectable disease. The *AJCC's Cancer Staging Manual*, *eighth edition*, definitions of TNM also include invasion of the azygos vein or peritoneum as T4a, potentially resectable disease [22]. With the use of preoperative therapy, some patients who seem to be unresectable at diagnosis could have a sufficient response to become resectable. A PET-CT before a curative resection decision is useful to detect interval distant metastasis to avoid an unuseful big operation [108].

Lymph node involvement in an area distant from the primary—for example, in the celiac area for a SCC in the upper or middle thoracic esophagus—was previously thought to be a distant metastatic disease, and patients were deferred from surgery. But in the eighth edition of the AJCC's TNM staging system, they are scored as regional lymph nodes, regardless of the tumor location and histology. Patients may be deemed unsuitable for surgery either because of disease extent or due to medical comorbidity or high cervical location. These patients without distant metastasis are treated with definitive CRT (dCRT). Definitive CRT is an effective and well-tolerated treatment, with survival rates in resectable patients similar to those in surgical series without preoperative CRT [109–111]. Yet, the prognosis and survival of unresectable inoperable esophageal cancer remain poor, with a 5-year survival of about 20% [109, 112]. After dCRT, almost 50% of patients develop a locoregional recurrence, and recurrence patterns differ from the pattern of recurrence after surgery [109, 113].

Cervical esophageal tumors are usually treated as head and neck SCCs because of the functional deficits and impairment in quality of life as a result of a definitive resection in that area. So resection is rarely a choice in the upfront treatment and mostly reserved for failures after definitive CRT.

For thoracic esophageal tumors, after assessment of resectability, locally advanced unresectable cancer is treated with definitive CRT rather than RT alone in patients who are thought to be able to tolerate it. For patients with SCC, the regimen used in the RTOG 85-01 and Intergroup 0123 trials (cisplatin–fluorouracil) is mostly chosen [28, 73], but FOLFOX can be an option. Weekly carboplatin and paclitaxel regimen may also be used. The optimal dose-fractionation schedule for RT is not obviously determined. The 50.4 Gy administered in 28 daily fractions as used in the RTOG 85-01 and INT 0123 studies is thought to be standard [72, 73]. The esophagus is surrounded by critical organs, so advanced radiation techniques can uniquely reduce unnecessary radiation exposure. Three-dimensional (3-D) conformal techniques should be used in treatment planning. Advanced radiation techniques are having clinical importance to avoid toxicities to nearby vital organs such as the heart, lungs, spinal cord, and liver. Larger volumes of radiation doses to these organs correlate with treatment-related toxicities such as pulmonary complications and cardiac toxicities. Even

when there is no level 1 evidence that supports the use of advanced technologies, such as intensity-modulated radiation therapy (IMRT), the use of IMRT was found in a population-based analysis to be significantly associated with lower all-cause mortality, cardiac mortality, and other-cause mortality in patients with EC [114]. Furthermore, despite the high cost, proton beam therapy could have a role in this field too.

Induction chemotherapy followed by dCRT can be an option for selected patients. It can provide significant relief of dysphagia before the start of CRT because nutrition is an important problem during CRT in patients with significant dysphagia before the start of therapy. A tube jejunostomy is the mostly used and most suitable method for such patients before the start of CRT. Induction chemotherapy can also have an effect on distant metastatic disease, which eventually develops in these locally advanced stage patients. Most trials evaluating this approach are made with potentially resectable patients.

In another study, the phase II RTOG 0113 trial, patients with localized esophageal cancer, SCC, or AC, who had unresectable disease, who were unwilling to undergo surgery, or who were medically unfit for surgery were included. Patients received either induction with fluorouracil, cisplatin, and paclitaxel and then fluorouracil plus paclitaxel with 50.4 Gy of radiation, or induction with paclitaxel plus cisplatin and then the same chemotherapy with 50.4 Gy of radiation. The second arm was without fluorouracil. The primary end point was to assess whether any approach would achieve a ≥77.5% 1-year survival rate, surpassing the historical 66% rate from the RTOG protocol 9405. Both arms were associated with high morbidity. The median survival time was 28.7 months for patients in arm A and 14.9 months for patients in arm B (18.8 months for patients in RTOG 9405). The 1-year survival rate of 75.7% in arm A was close to, but did not meet or surpass, the 77.5% goal. The 2-year survival rate was 56% for arm A and 37% for arm B [115]. So neither approach was superior to the historic control of INT 123/RTOG 9405 and toxicity was increased.

Management of Metastatic Disease

Goals of treatment in a metastatic setting patient should be to palliate symptoms, especially dysphagia and anorexia; improve quality of life; and prolong survival. In 2006, a Cochrane review assessed RTCs comparing chemotherapy versus best supportive care or different chemotherapy regimens against each other in patients with metastatic carcinoma of the esophagus or EGJ tumors. Due to variations in patient population and chemotherapy regimens, it was not possible to make a conclusion about the effectiveness of chemotherapy against best supportive care. Analysis of the studies comparing different chemotherapy regimens concluded that there was no consistent benefit with any specific chemotherapy regimen. Chemotherapy agents with promising response rates and tolerable toxicity were cisplatin, fluorouracil, paclitaxel, and anthracyclines [116]. From trials of advanced gastric cancer, as we can see a significant survival benefit in favor of chemotherapy versus best supportive care [117], agents used in advanced gastric cancer are recommended for ACs of the esophagus and EGJ tumors. So HER-2 overexpression should be determined for patients who can be candidates for trastuzumab therapy. HER-2 overexpressing tumors should be treated with trastuzumab and cisplatin–fluorouracil or cisplatin–capecitabine as in the ToGA trial [118]. For patients whose tumors do not express HER-2, options are combined chemotherapy regimens of platinum/fluoropyrimidines with taxanes or anthracyclines—docetaxel, cisplatin, fluorouracil (DCF); ECF; ECX; epirubicin, cisplatin, capecitabine (EOX)—if the patient is fit enough to tolerate it [119, 120]. Doublet regimens may also be good options as we think continuum of care of these patients and leaving taxanes to second-line treatment. As for doublet regimens, FOLFOX/XELOX (capecitabine instead of fluorouracil, folinic acid) or cisplatin–fluorouracil or cisplatin–capecitabine can be options. For older or unfit patients, single agents such as fluoropyrimidines (capecitabine, S1, infusional fluorouracil+folinic acid), weekly paclitaxel, or irinotecan may be options. In continuum of care of esophagogastric AC: If progression is seen 3 months after first-line platinum/fluoropirimidine +/− epirubicin therapy, rechallenge with platinum and fluoropirimidines can be contemplated. In this study, median PFS and OS from rechallenge are 3.9 and 6.6 months, respectively [121]. Two pivotal randomized controlled trials established advantage of second or subsequent lines of chemotherapy versus best supportive care in advanced esophagogastric cancer patients [122, 123]. A meta-analysis also has shown survival benefit [124]. In these trials, second-line chemotherapy options were docetaxel or irinotecan. Weekly paclitaxel is also an acceptable option for second-line therapy [125, 126]. In the REGARD study, a placebo-controlled phase III trial, an antiangiogenic agent ramucirumab has shown benefit as a single agent in second-line therapy [127]. In the RAINBOW study, ramucirumab when combined with weekly paclitaxel showed a median OS of 9.6 months versus 7.4 months with single-agent paclitaxel in second line after platinum fluoropirimidine chemotherapy [128]. In a chemotherapy refractory group (two or more lines) of patients, apatinib—a novel vasculo-endothelial growth factor receptor-2 tyrosine kinase inhibitor—showed improvement in OS compared to placebo [129].

Immunotherapeutic agents, check point inhibitors, also show promise for esophagogastric cancers as with other gastrointestinal system tumors. Anti-PD-1 antibodies, nivolumab, and pembrolizumab had shown activity in pre-

treated patients with advanced gastric and EGJ AC. In the ATTRACTION II study, patients on nivolumab had improved 1-year OS compared to placebo (26% vs 11%) in Asian advanced gastric and EGJ AC patients who had two or more previous chemotherapy regimens. In this study, patients are not selected by PD-L1 expression [130]. The Checkmate 032 trial investigated nivolumab alone or in combination with ipilimumab, again in pretreated patients, but this time in a Western population, and the trial had shown similar results with 1-year OS of 36% [131]. The Keynote 059 study is a multicohort phase II study. In cohort 1, previously treated patients received pembrolizumab. In the all-patient population, the overall response rate (ORR) is %11.6; PDL-1(+) patients had an ORR of 15.5%; PDL-1(−) patients had an ORR of 6.4%; and in MSI high patients (accounts for 4% of patients), the 1-year ORR is 57%, with a CR rate of 14% in this subgroup [132]. In cohort 2, patients received no prior therapy. Pembrolizumab is given in combination with cisplatin–fluorouracil or capecitabine. All patients had experienced a reduction in target lesion size in the waterfall plot. Responses were independent of PDL-1 expression. Median OS was 20.8 months [133].

For patients with advanced SCC, commonly used agents include platinum, fluoropyrimidine agents, and taxanes, though they are associated with limited clinical benefit. DCF can be the first choice for fit patients. Cisplatin–fluorouracil, cisplatin–capecitabine, FOLFOX, and XELOX can be options. There are also immunotherapy trials with check point inhibitors for esophageal SCCs. Pembrolizumab, an anti-PD-1 antibody, was active in pretreated esophageal cancer patients with PD-L1-expressing tumors (>1% PD-L1-positive tumor cells and/or tumor stroma), with a partial response (PR) rate of 30.4% (40.0% for adenocarcinoma, 29.4% for squamous cell) [134]. In an open-label, single-arm, multicenter phase II trial, patients with advanced esophageal SCC—who progressed after or were intolerant to fluoropyrimidine-based, platinum-based, and taxane-based chemotherapy regimens—were treated with nivolumab. The proportion of patients who achieved centrally assessed disease control was 27%. Nivolumab showed promising activity with a manageable safety profile. This drug could offer a potential new treatment approach for patients with treatment-refractory advanced squamous cell carcinoma [135].

Palliative Management of Dysphagia

Endoscopic therapy is important for palliating obstructive symptoms. Dilation using balloons or bougies and placement of a stent through the narrowed segment may relieve dysphagia. Covered self-expandable metal stents are widely used for this purpose [136, 137]. These techniques can be used in nonoperable patients and for patients who need palliation of dysphagia before a definitive therapy with CRT or surgery. Percutaneous gastrostomy for clearly unresectable patients or jejunostomies for other patients also may be options.

References

1. Anonymous. Estimated cancer incidence, mortality and prevalence worldwide in 2012. www.globocan.iarc.fr; Globocan 2012.
2. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut. 2015;64(3):381–7.
3. Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, et al. Trends in esophageal adenocarcinoma incidence and mortality. Cancer. 2013;119(6):1149–58.
4. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? Cancer Epidemiol Biomark Prev. 2010;19(6):1468–70.
5. Rubenstein JH, Shaheen NJ. Epidemiology, diagnosis, and management of esophageal adenocarcinoma. Gastroenterology. 2015;149(2):302–17 e301.
6. Dolan K, Sutton R, Walker SJ, Morris AI, Campbell F, Williams EM. New classification of oesophageal and gastric carcinomas derived from changing patterns in epidemiology. Br J Cancer. 1999;80(5-6):834–42.
7. SEER 18 2006–2012.
8. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol. 2007;165(12):1424–33.
9. Akhtar S, Sheikh AA, Qureshi HU. Chewing areca nut, betel quid, oral snuff, cigarette smoking and the risk of oesophageal squamous-cell carcinoma in South Asians: a multicentre case-control study. Eur J Cancer. 2012;48(5):655–61.
10. Islami F, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F. High-temperature beverages and foods and esophageal cancer risk – a systematic review. Int J Cancer. 2009;125(3):491–524.
11. Li X, Gao C, Yang Y, Zhou F, Li M, Jin Q, et al. Systematic review with meta-analysis: the association between human papillomavirus infection and oesophageal cancer. Aliment Pharmacol Ther. 2014;39(3):270–81.
12. Chaber-Ciopinska A, Kiprian D, Kawecki A, Kaminski MF. Surveillance of patients at high-risk of squamous cell esophageal cancer. Best Pract Res Clin Gastroenterol. 2016;30(6):893–900.
13. Wright E, Schofield PT, Molokhia M. Bisphosphonates and evidence for association with esophageal and gastric cancer: a systematic review and meta-analysis. BMJ Open. 2015;5(12):e007133.
14. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. JAMA. 2013;310(6):627–36.
15. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international beacon consortium. J Natl Cancer Inst. 2010;102(17):1344–53.
16. Cook MB, Greenwood DC, Hardie LJ, Wild CP, Forman D. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. Am J Gastroenterol. 2008;103(2):292–300.
17. Thrift AP, Shaheen NJ, Gammon MD, Bernstein L, Reid BJ, Onstad L, et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. J Natl Cancer Inst. 2014;106(11):dju252.
18. Newton M, Bryan R, Burnham WR, Kamm MA. Evaluation of Helicobacter pylori in reflux oesophagitis and Barrett's oesophagus. Gut. 1997;40(1):9–13.

19. Loffeld RJ, Ten Tije BJ, Arends JW. Prevalence and significance of Helicobacter pylori in patients with Barrett's esophagus. Am J Gastroenterol. 1992;87(11):1598–600.
20. Rokkas T, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. Relationship between Helicobacter pylori infection and esophageal neoplasia: a meta-analysis. Clin Gastroenterol Hepatol. 2007;5(12):1413–7, 1417 e1411-1412.
21. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg. 1998;85(11):1457–9.
22. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Ann Cardiothorac Surg. 2017;6(2):119–30.
23. Rice TW, Chen LQ, Hofstetter WL, Smithers BM, Rusch VW, Wijnhoven BP, et al. Worldwide esophageal cancer collaboration: pathologic staging data. Dis Esophagus. 2016;29(7):724–33.
24. Rice TW, Apperson-Hansen C, DiPaola LM, Semple ME, Lerut TE, Orringer MB, et al. Worldwide esophageal cancer collaboration: clinical staging data. Dis Esophagus. 2016;29(7):707–14.
25. Rice TW, Lerut TE, Orringer MB, Chen LQ, Hofstetter WL, Smithers BM, et al. Worldwide esophageal cancer collaboration: Neoadjuvant pathologic staging data. Dis Esophagus. 2016;29(7):715–23.
26. Rice TW, Kelsen DP, Blackstone EH, et al. Esophagus and esophagogastric junction. In: Amin MB, Edge SB, Greene FL, et al., editors. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017. p. 185–202.
27. Al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol. 1997;15(1):277–84.
28. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation therapy oncology group. JAMA. 1999;281(17):1623–7.
29. Pennathur A, Farkas A, Krasinskas AM, Ferson PF, Gooding WE, Gibson MK, et al. Esophagectomy for t1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. Ann Thorac Surg. 2009;87(4):1048–54.. discussion 1054-1045.
30. Pech O, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut. 2008;57(9):1200–6.
31. Markar SR, Mackenzie H, Ni M, Huddy JR, Askari A, Faiz O, et al. The influence of procedural volume and proficiency gain on mortality from upper GI endoscopic mucosal resection. Gut. 2018;67(1):79–85.
32. Mannath J, Ragunath K. Role of endoscopy in early oesophageal cancer. Nat Rev Gastroenterol Hepatol. 2016;13(12):720–30.
33. Ell C, May A, Pech O, Gossner L, Guenter E, Behrens A, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc. 2007;65(1):3–10.
34. Pech O, Gossner L, May A, Vieth M, Stolte M, Ell C. Endoscopic resection of superficial esophageal squamous-cell carcinomas: Western experience. Am J Gastroenterol. 2004;99(7):1226–32.
35. Sgourakis G, Gockel I, Lang H. Endoscopic and surgical resection of t1a/t1b esophageal neoplasms: a systematic review. World J Gastroenterol. 2013;19(9):1424–37.
36. Manner H, May A, Pech O, Gossner L, Rabenstein T, Gunter E, et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol. 2008;103(10):2589–97.
37. Sun F, Yuan P, Chen T, Hu J. Efficacy and complication of endoscopic submucosal dissection for superficial esophageal carcinoma: a systematic review and meta-analysis. J Cardiothorac Surg. 2014;9:78.
38. Nakagawa K, Koike T, Iijima K, Shinkai H, Hatta W, Endo H, et al. Comparison of the long-term outcomes of endoscopic resection for superficial squamous cell carcinoma and adenocarcinoma of the esophagus in Japan. Am J Gastroenterol. 2014;109(3):348–56.
39. www.nccn.org. NCCN guidelines, version 2.2016, esophageal and esophagogastric junction tumors.
40. Pech O, Bollschweiler E, Manner H, Leers J, Ell C, Holscher AH. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. Ann Surg. 2011;254(1):67–72.
41. Prasad GA, Wu TT, Wigle DA, Buttar NS, Wongkeesong LM, Dunagan KT, et al. Endoscopic and surgical treatment of mucosal (t1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology. 2009;137(3):815–23.
42. Das A, Singh V, Fleischer DE, Sharma VK. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. Am J Gastroenterol. 2008;103(6):1340–5.
43. Chadwick G, Groene O, Markar SR, Hoare J, Cromwell D, Hanna GB. Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events. Gastrointest Endosc. 2014;79(5):718–31 e713.
44. Pech O, May A, Manner H, Behrens A, Pohl J, Weferling M, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology. 2014;146(3):652–60 e651.
45. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009;360(22):2277–88.
46. Shaheen NJ, Overholt BF, Sampliner RE, Wolfsen HC, Wang KK, Fleischer DE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. 2011;141(2):460–8.
47. Bergman JJ, Zhang YM, He S, Weusten B, Xue L, Fleischer DE, et al. Outcomes from a prospective trial of endoscopic radiofrequency ablation of early squamous cell neoplasia of the esophagus. Gastrointest Endosc. 2011;74(6):1181–90.
48. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462–7.
49. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26(7):1086–92.
50. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
51. Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32(23):2416–22.
52. Czito BG, Palta M, Willett CG. Results of the FFCD 9901 trial in early-stage esophageal carcinoma: is it really about neoadjuvant therapy? J Clin Oncol. 2014;32(23):2398–400.
53. Kato H, Tachimori Y, Watanabe H, Itabashi M, Hirota T, Yamaguchi H, et al. Intramural metastasis of thoracic esophageal carcinoma. Int J Cancer. 1992;50(1):49–52.
54. Hosch SB, Stoecklein NH, Pichlmeier U, Rehders A, Scheunemann P, Niendorf A, et al. Esophageal cancer: the mode of lymphatic tumor cell spread and its prognostic significance. J Clin Oncol. 2001;19(7):1970–5.
55. Nigro JJ, Hagen JA, DeMeester TR, DeMeester SR, Peters JH, Oberg S, et al. Prevalence and location of nodal metastases in distal

esophageal adenocarcinoma confined to the wall: implications for therapy. J Thorac Cardiovasc Surg. 1999;117(1):16–23.. discussion 23-15.
56. Stein HJ, Hutter J, Feith M, von Rahden BH. Limited surgical resection and jejunal interposition for early adenocarcinoma of the distal esophagus. Semin Thorac Cardiovasc Surg. 2007;19(1):72–8.
57. Barbour AP, Rizk NP, Gonen M, Tang L, Bains MS, Rusch VW, et al. Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome. Ann Surg. 2007;246(1):1–8.
58. Ito H, Clancy TE, Osteen RT, Swanson RS, Bueno R, Sugarbaker DJ, et al. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg. 2004;199(6):880–6.
59. Daiko H, Hayashi R, Saikawa M, Sakuraba M, Yamazaki M, Miyazaki M, et al. Surgical management of carcinoma of the cervical esophagus. J Surg Oncol. 2007;96(2):166–72.
60. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725–30.
61. Bedard EL, Inculet RI, Malthaner RA, Brecevic E, Vincent M, Dar R. The role of surgery and postoperative chemoradiation therapy in patients with lymph node positive esophageal carcinoma. Cancer. 2001;91(12):2423–30.
62. Adelstein DJ, Rice TW, Rybicki LA, Saxton JP, Videtic GM, Murthy SC, et al. Mature results from a phase II trial of postoperative concurrent chemoradiotherapy for poor prognosis cancer of the esophagus and gastroesophageal junction. J Thorac Oncol. 2009;4(10):1264–9.
63. Chen J, Pan J, Liu J, Li J, Zhu K, Zheng X, et al. Postoperative radiation therapy with or without concurrent chemotherapy for node-positive thoracic esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2013;86(4):671–7.
64. Tachibana M, Yoshimura H, Kinugasa S, Shibakita M, Dhar DK, Ueda S, et al. Postoperative chemotherapy vs chemoradiotherapy for thoracic esophageal cancer: a prospective randomized clinical trial. Eur J Surg Oncol. 2003;29(7):580–7.
65. Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan clinical oncology group study--JCOG9204. J Clin Oncol. 2003;21(24):4592–6.
66. Speicher PJ, Englum BR, Ganapathi AM, Mulvihill MS, Hartwig MG, Onaitis MW, et al. Adjuvant chemotherapy is associated with improved survival after esophagectomy without induction therapy for node-positive adenocarcinoma. J Thorac Oncol. 2015;10(1):181–8.
67. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol. 2012;19(1):68–74.
68. Campbell NP, Villaflor VM. Neoadjuvant treatment of esophageal cancer. World J Gastroenterol. 2010;16(30):3793–803.
69. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349(23):2241–52.
70. Rice TW, Rusch VW, Apperson-Hansen C, Allen MS, Chen LQ, Hunter JG, et al. Worldwide esophageal cancer collaboration. Dis Esophagus. 2009;22(1):1–8.
71. Sykes AJ, Burt PA, Slevin NJ, Stout R, Marrs JE. Radical radiotherapy for carcinoma of the oesophagus: an effective alternative to surgery. Radiother Oncol. 1998;48(1):15–21.
72. Herskovic A, Martz K, Al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326(24):1593–8.
73. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. Int 0123 (radiation therapy oncology group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20(5):1167–74.
74. Wong RK, Malthaner R. Withdrawn. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. Cochrane Database Syst Rev. 2010;(1):CD002092.
75. Conroy T, Galais MP, Raoul JL, Bouche O, Gourgou-Bourgade S, Douillard JY, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol. 2014;15(3):305–14.
76. Honing J, Smit JK, Muijs CT, Burgerhof JG, de Groot JW, Paardekooper G, et al. A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. Ann Oncol. 2014;25(3):638–43.
77. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (cross): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090–8.
78. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681–92.
79. Kranzfelder M, Schuster T, Geinitz H, Friess H, Buchler P. Meta-analysis of neoadjuvant treatment modalities and definitive non-surgical therapy for oesophageal squamous cell cancer. Br J Surg. 2011;98(6):768–83.
80. Rohatgi PR, Swisher SG, Correa AM, Wu TT, Liao Z, Komaki R, et al. Failure patterns correlate with the proportion of residual carcinoma after preoperative chemoradiotherapy for carcinoma of the esophagus. Cancer. 2005;104(7):1349–55.
81. Ancona E, Ruol A, Santi S, Merigliano S, Sileni VC, Koussis H, et al. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone. Cancer. 2001;91(11):2165–74.
82. Kleinberg L, Knisely JP, Heitmiller R, Zahurak M, Salem R, Burtness B, et al. Mature survival results with preoperative cisplatin, protracted infusion 5-fluorouracil, and 44-Gy radiotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2003;56(2):328–34.
83. Wang CC, Cheng JC, Tsai CL, Lee JM, Huang PM, Lin CC, et al. Pathological stage after neoadjuvant chemoradiation and esophagectomy superiorly predicts survival in patients with esophageal squamous cell carcinoma. Radiother Oncol. 2015;115(1):9–15.
84. Berger AC, Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol. 2005;23(19):4330–7.
85. Scheer RV, Fakiris AJ, Johnstone PA. Quantifying the benefit of a pathologic complete response after neoadjuvant chemoradiotherapy in the treatment of esophageal cancer. Int J Radiat Oncol Biol Phys. 2011;80(4):996–1001.
86. Ajani JA, Komaki R, Putnam JB, Walsh G, Nesbitt J, Pisters PW, et al. A three-step strategy of induction chemotherapy then chemoradiation followed by surgery in patients with potentially resectable carcinoma of the esophagus or gastroesophageal junction. Cancer. 2001;92(2):279–86.
87. Swisher SG, Ajani JA, Komaki R, Nesbitt JC, Correa AM, Cox JD, et al. Long-term outcome of phase II trial evaluating chemotherapy, chemoradiotherapy, and surgery for locoregionally advanced esophageal cancer. Int J Radiat Oncol Biol Phys. 2003;57(1):120–7.

88. Ajani JA, Walsh G, Komaki R, Morris J, Swisher SG, Putnam JB Jr, et al. Preoperative induction of CPT-11 and cisplatin chemotherapy followed by chemoradiotherapy in patients with locoregional carcinoma of the esophagus or gastroesophageal junction. Cancer. 2004;100(11):2347–54.
89. Pasini F, de Manzoni G, Zanoni A, Grandinetti A, Capirci C, Pavarana M, et al. Neoadjuvant therapy with weekly docetaxel and cisplatin, 5-fluorouracil continuous infusion, and concurrent radiotherapy in patients with locally advanced esophageal cancer produced a high percentage of long-lasting pathological complete response: a phase 2 study. Cancer. 2013;119(5):939–45.
90. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851–6.
91. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. Pet to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007;8(9):797–805.
92. zum Buschenfelde CM, Herrmann K, Schuster T, Geinitz H, Langer R, Becker K, et al. (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. J Nucl Med. 2011;52(8):1189–96.
93. Goodman KA, Hall N, Bekaii-Saab TS, Ou F-S, Twohy E, Meyers MO, Boffa DJ, Mitchell K, Perry K, Frankel WL, Venook AP, O'Reilly EM, Ilson DH. Survival outcomes from CALGB 80803 (Alliance): a randomized phase II trial of PET scan-directed combined modality therapy for esophageal cancer. J Clin Oncol. 2018;36(15_suppl):4012.
94. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23(10):2310–7.
95. Stahl M, Wilke H, Lehmann N, et al. Long-term results of a phase III study investigating chemoradiation with and without surgery in locally advanced squamous cell carcinoma (LA-SCC) of the esophagus (abstract). J Clin Oncol, 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2008;26(15S (May 20 Supplement)):4530.
96. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007;25(10):1160–8.
97. Bonnetain F, Bouche O, Michel P, Mariette C, Conroy T, Pezet D, et al. A comparative longitudinal quality of life study using the spitzer quality of life index in a randomized multicenter phase III trial (FFCD 9102): Chemoradiation followed by surgery compared with chemoradiation alone in locally advanced squamous resectable thoracic esophageal cancer. Ann Oncol. 2006;17(5):827–34.
98. Vincent J, Mariette C, Pezet D, Huet E, Bonnetain F, Bouche O, et al. Early surgery for failure after chemoradiation in operable thoracic oesophageal cancer. Analysis of the non-randomised patients in FFCD 9102 phase III trial: Chemoradiation followed by surgery versus chemoradiation alone. Eur J Cancer. 2015;51(13):1683–93.
99. Best LM, Mughal M, Gurusamy KS. Non-surgical versus surgical treatment for oesophageal cancer. Cochrane Database Syst Rev. 2016;(3):CD011498.
100. Shridhar R, Freilich J, Hoffe SE, Almhanna K, Fulp WJ, Yue B, et al. Single-institution retrospective comparison of preoperative versus definitive chemoradiotherapy for adenocarcinoma of the esophagus. Ann Surg Oncol. 2014;21(12):3744–50.
101. Sudo K, Xiao L, Wadhwa R, Shiozaki H, Elimova E, Taketa T, et al. Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. J Clin Oncol. 2014;32(30):3400–5.
102. Cheedella NK, Suzuki A, Xiao L, Hofstetter WL, Maru DM, Taketa T, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort. Ann Oncol. 2013;24(5):1262–6.
103. Monjazeb AM, Riedlinger G, Aklilu M, Geisinger KR, Mishra G, Isom S, et al. Outcomes of patients with esophageal cancer staged with [(1)(8)F]fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? J Clin Oncol. 2010;28(31):4714–21.
104. Piessen G, Petyt G, Duhamel A, Mirabel X, Huglo D, Mariette C. Ineffectiveness of (1)(8)F-fluorodeoxyglucose positron emission tomography in the evaluation of tumor response after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg. 2013;258(1):66–76.
105. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
106. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715–21.
107. Al-Batran SE, Homann N, Schmalenberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. In: ASCO 2017 Annual Meeting. 2017: Abstract 4004.
108. Bruzzi JF, Swisher SG, Truong MT, Munden RF, Hofstetter WL, Macapinlac HA, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. Cancer. 2007;109(1):125–34.
109. Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemoradiation for oesophageal cancer--a standard of care in patients with non-metastatic oesophageal cancer. Clin Oncol. 2011;23(3):182–8.
110. Teoh AY, Chiu PW, Yeung WK, Liu SY, Wong SK, Ng EK. Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: results from a randomized controlled trial. Ann Oncol. 2013;24(1):165–71.
111. Medical Research Council Oesophageal Cancer Working G. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727–33.
112. Tougeron D, Di Fiore F, Hamidou H, Rigal O, Paillot B, Michel P. Response to definitive chemoradiotherapy and survival in patients with an oesophageal adenocarcinoma versus squamous cell carcinoma: a matched-pair analysis. Oncology. 2007;73(5–6):328–34.
113. Versteijne E, van Laarhoven HW, van Hooft JE, van Os RM, Geijsen ED, van Berge Henegouwen MI, et al. Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: Locoregional recurrence pattern. Dis Esophagus. 2015;28(5):453–9.
114. Lin SH, Zhang N, Godby J, Wang J, Marsh GD, Liao Z, et al. Radiation modality use and cardiopulmonary mortality risk in elderly patients with esophageal cancer. Cancer. 2016;122(6):917–28.
115. Ajani JA, Winter K, Komaki R, Kelsen DP, Minsky BD, Liao Z, et al. Phase II randomized trial of two nonoperative regimens of

induction chemotherapy followed by chemoradiation in patients with localized carcinoma of the esophagus: RTOG 0113. J Clin Oncol. 2008;26(28):4551–6.
116. Homs MY, vd Gaast A, Siersema PD, Steyerberg EW, Kuipers EJ. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. Cochrane Database Syst Rev. 2006;(4):CD004063.
117. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2010;(3):CD004064.
118. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
119. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358(1):36–46.
120. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the v325 study group. J Clin Oncol. 2006;24(31):4991–7.
121. Okines AF, Asghar U, Cunningham D, Ashley S, Ashton J, Jackson K, et al. Rechallenge with platinum plus fluoropyrimidine +/− epirubicin in patients with oesophagogastric cancer. Oncology. 2010;79(1–2):150–8.
122. Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol. 2012;30(13):1513–8.
123. Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (cougar-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15(1):78–86.
124. Janowitz T, Thuss-Patience P, Marshall A, Kang JH, Connell C, Cook N, et al. Chemotherapy vs supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data. Br J Cancer. 2016;114(4):381–7.
125. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013;31(35):4438–44.
126. Tarazona N, Smyth EC, Peckit C, Chau I, Watkins D, Rao S, et al. Efficacy and toxicity of salvage weekly paclitaxel chemotherapy in non-Asian patients with advanced oesophagogastric adenocarcinoma. Ther Adv Med Oncol. 2016;8(2):104–12.
127. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (regard): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9.
128. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (rainbow): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224–35.
129. Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, et al. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol. 2016;34(13):1448–54.
130. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10111):2461–71.
131. Janjigian YY, Ott PA, Calvo E, et al. Nivolumab ± ipilimumab in patients with advanced/metastatic chemotherapy-refractory gastric, esophageal, or gastroesophageal junction cancer: Checkmate 032 study. In: ASCO 2017 Annual Meeting. 2017; Abstract 4014.
132. Fuchs CS, Doi T, Jang RW, et al. Efficacy and safety of pembrolizumab monotherapy in patients with previously treated advanced gastric cancer: KEYNOTE 059 study-cohort 1. In: ASCO 2017 Annual Meeting. 2017; Abstract 4003.
133. Bang YJ, Muro K, Fuchs CS, et al. KEYNOTE-059 cohort 2: Safety and efficacy of pembrolizumab (pembro) plus 5-fluorouracil (5-FU) and cisplatin for first-line (1L) treatment of advanced gastric cancer. In: ASCO 2017 Annual Meeting. 2017; Abstract 4012.
134. Doi T, Piha-Paul SA, Jalal SI, Mai-Dang H, Yuan S, Koshiji M, Csiki I, Bennouna J. Pembrolizumab (MK-3475) for patients (pts) with advanced esophageal carcinoma: preliminary results from KEYNOTE-028. J Clin Oncol. 2015;33(15_suppl):4010.
135. Kudo T, Hamamoto Y, Kato K, Ura T, Kojima T, Tsushima T, et al. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. Lancet Oncol. [Clinical Trial, Phase II Multicenter Study]. 2017;18(5):631–9.
136. Battersby NJ, Bonney GK, Subar D, Talbot L, Decadt B, Lynch N. Outcomes following oesophageal stent insertion for palliation of malignant strictures: a large single centre series. J Surg Oncol. 2012;105(1):60–5.
137. Stewart DJ, Balamurugan R, Everitt NJ, Ravi K. Ten-year experience of esophageal self-expanding metal stent insertion at a single institution. Dis Esophagus. 2013;26(3):276–81.

Gastric Cancer

5

Yung-Jue Bang, Do-Youn Oh, Han-Kwang Yang, Sang Gyun Kim, and Woo-Ho Kim

Epidemiology and Etiology

Gastric cancer is the fifth most common cancer and the third leading cause of death, accounting for 9% of the total cancer mortality in the world [1]. Gastric cancer is much more prevalent in East Asia, and more than 60% of cases occur in this region, and is less common in Western Europe, North America, and Africa. The incidence rate is twice as high in men as in women. The incidence of non-cardia gastric cancer has declined worldwide. However, the incidence of gastric adenocarcinoma in cardia has increased, especially in Western countries, which may be associated with widespread chronic gastroesophageal reflux disease (GERD) and obesity.

Gastric cancer develops as a multi-step process and both environmental and genetic factors contribute. Among environmental factors, *Helicobacter pylori* infection is most important. *H. pylori* is a Gram-negative bacillus that colonizes the gastric mucosa, and has been categorized as a Group 1 carcinogen for gastric cancer since 1994. The prevalence of *H. pylori* varies with regions, age, and socioeconomic environment. In developing countries, the prevalence of *H. pylori* infection is up to 80% in adults, whereas it is less than 30% in Western countries [2]. Although *H. pylori* accounts for 60% of gastric cancer, most people with *H. pylori* infection remain asymptomatic lifelong, and fewer than 0.5% with *H. pylori* infection suffer from gastric cancer [3].

H. pylori produces many virulence factors that regulate gastric inflammation and carcinogenesis via epithelial intracellular signaling pathways. CagA (cytotoxin-associated gene A) and VacA (vacuolating cytotoxin A) are the major virulence factors of *H. pylori*, and associated with increased risk of gastric carcinogenesis [4]. *H. pylori* upregulates various pro-inflammatory cytokines—such as interleukin (IL)-1, IL-6, and IL-8; tumor necrosis factor-alpha (TNF-α[alpha]); and regulated on activation, normal T cell expressed and secreted (RANTES)—which leads to over-proliferation and apoptosis of the gastric epithelial cells, and increases the risk of DNA damage and chromosomal mutations by highly expressed reactive oxygen species (ROS) and nitrogen species (RNS) [5].

P53 is a major tumor suppressor gene and dysregulated in the gastric carcinogenesis by *H. pylori* infection. Dysregulation of mutated p53 is commonly found in gastric cancer, especially with CagA-positive *H. pylori*. Inactivation of p53 induces impaired apoptosis, which can lead to the sustained proliferation of the gastric epithelial cells with aberrant DNA damage [6].

Epigenetic alterations are frequent in the gastric carcinogenesis. Methylation, point mutation, recombination, deletion, and duplication are the common forms of alteration, and the CpG islands hypermethylation is the most common epigenetic change in tumor suppressor genes [7]. MicroRNA also has been implicated in *H. pylori*-induced chronic inflammation and gastric carcinogenesis by CagA [8]. Chronic *H. pylori* infection promotes the progression from atrophic gastritis, intestinal metaplasia, and dysplasia to carcinoma. Atrophy/intestinal metaplasia has been known to be a preneoplastic change [9].

Other environmental factors include diet and lifestyle. High intake of preserved food in salt, fat, and N-nitroso compound is associated with an increased risk factor of gastric cancer, whereas fresh fruit, vegetables, and fiber decrease the risk of gastric cancer [10]. N-nitroso compounds are formed

Y.-J. Bang (✉) · D.-Y. Oh
Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea
e-mail: bangyj@snu.ac.kr

H.-K. Yang
Department of Surgery, Gastric Cancer Center, Seoul National University Hospital, Seoul, Republic of Korea

S. G. Kim
Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul, Republic of Korea

W.-H. Kim
Department of Pathology, Molecular Pathology Center, Seoul National University Hospital, Seoul, Republic of Korea

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_5

in the process of preservation of nitrate or nitrite, and are rich in cured meats, broiled fish with flame, instant foods, and dried milk. Salty foods such as salty fish and meat, pickled vegetables, and soy sauce can induce direct damage to the gastric mucosa and increase the risk of *H. pylori*-induced chronic inflammation [11]. Fruits and vegetables rich in vitamin C, carotenoid, folate, and phytochemicals may modestly reduce the risk of gastric cancer [11].

Smoking and alcohol are known to be established risk factors of gastric cancer [12]. Smoking induces the premalignant lesion in the gastric mucosa, and increases the risk of persistent *H. pylori* infection. Alcohol has a role in the gastric carcinogenesis as a gastric irritant. Chronic gastroesophageal reflux with obesity is associated with increased risk of gastric cancer in cardia [13]. Epstein–Barr virus (EBV) infection is also related to gastric carcinogenesis [12].

A family history of gastric cancer has been known to be associated with increased risk, with an odds ratio between 2 and 10 [14]. In Western countries, the family members of patients with gastric cancer tend to have an increased rate of *H. pylori* infection and chronic mucosal inflammation [15]. Although *H. pylori* eradication is recommended in the European guidelines, the effect of cancer prevention has not been fully clarified [16]. In East Asia, most cases of gastric cancer with a family history are sporadic rather than inherited [17].

Pathology

Gastric cancer is divided into early cancer and advanced cancer according to the depth of tumor invasion. Early cancer, representing the mucosal or submucosal involvement, is characterized by excellent prognosis. Early cancers comprise more than 70% of surgically or endoscopically resected gastric carcinomas in Japan and Korea where screening programs are active. However, in other countries, the frequency is much lower.

Grossly, advanced carcinoma is classified as polypoid, ulcero-fungating, ulcero-infiltrative, and diffusely infiltrative, as proposed by Borrmann. Histologically, the intestinal type based on Lauren's criteria is characterized by gland formation and the diffuse type is characterized by poorly cohesive cells. The mixed type is used when the quantity of intestinal and diffuse components is almost equal. The indeterminate type includes undifferentiated histology. The World Health Organization (WHO) classification recognizes five common types and several rare types. Common types include tubular, papillary, mucinous, poorly cohesive, and mixed types. Papillary or tubular carcinoma is graded into well, moderately, or poorly differentiated histology. The histologic grading is not well correlated with prognosis or recurrence rate. Mixed carcinoma, usually composed of papillo-tubular and poorly cohesive carcinoma, showed the clonality [18], and the phenotypic diversity is caused by somatic mutation of the CDH1 gene [19]. Neuroendocrine carcinoma is divided into large cell and small cell types. This histologic classification is common to all gastrointestinal tracts and the lungs. In gastric adenocarcinoma, it is common to see the cancer cells positively stained with neuroendocrine markers such as chromogranin A or synaptophysin. Mixed adenoneuroendocrine carcinoma (MANEC) is used only when at least 30% of the tumor area is occupied by tumor cells positive for neuroendocrine marker. If a minor portion—less than 30%—is composed of neuroendocrine carcinoma, the case is classified as conventional adenocarcinoma. Rare variants, which occupy less than 5%, include adenosquamous carcinoma, squamous cell carcinoma, hepatoid adenocarcinoma, germ cell carcinomas, undifferentiated carcinoma, etc.

Gastric cancer can be categorized into gastric or intestinal type by mucin expression [20]. MUC5AC or MUC6 are expressed in gastric type, and MUC2 or CD10 are expressed in intestinal type. Mixed type gastric cancer is characterized by expression of both markers, and the unclassified type is characterized by the absence of both markers. This classification is helpful for prognostic purpose, showing worst prognosis in gastric histology, but is not widely used outside Japan.

Adenocarcinoma of the esophagogastric junction (EGJ) attracts attention because of recently increased incidence, especially in Eastern countries. This tumor is defined as adenocarcinomas that cross the EGJ and the epicenter of carcinoma is within 2 cm from the EGJ. However, the definition of this classification is not always clear because the EGJ is blurred, especially for the cases when the carcinoma exists near the EGJ or has developed from Barrett's esophagus. Furthermore, the landmark for the EGJ is different for endoscopists, surgeons, and pathologists. The Union for International Cancer Control (UICC) recommends that the staging classification of EGJ cancer should follow esophageal cancer. In fact, the molecular and pathologic characteristics of EGJ adenocarcinoma are closer to gastric cancer rather than esophageal cancer.

Gastric carcinomas spread early to the regional lymph nodes, and the number of involved lymph nodes affects the prognosis of the patients. The lymph node involvement by carcinoma cells is divided into three categories: isolated tumor cells (ITC) when the tumor deposit is not greater than 0.2 mm, micrometastasis (greater than 0.2 mm but not greater than 2.0 mm), and macrometastasis (greater than 2.0 mm). The UICC guideline for counting the metastatic (positive) lymph nodes includes metastasis and micrometastasis but excluding the ITC. The recent meta-analysis revealed that the presence of micrometastasis is prognostically significant only in Eastern countries, but not in Western countries [21]. There is no convincing evidence that ITC is prognostically significant [22].

Neuroendocrine tumor (NET) is classified into three grades according to the mitosis count and Ki-67 index, but grade 3 is very rare. Gastric NET can be further subdivided into three types. Type I originates in a hypergastrinemic environment and follows a benign course. Type II exhibits more aggressive behavior with a 30% chance of distant metastasis. Type III has a 50% chance of distant metastasis and occurs in normogastric state. Evidence for progression from NET to neuroendocrine carcinoma has only rarely been reported, and most evidence indicates that neuroendocrine carcinoma is distinct from NET.

Hereditary diffuse gastric cancer is known to be caused by germline mutation of the CDH1 gene encoding tumor suppressor protein E-cadherin. Heterozygous germline mutation of CDH1 increases the risk of developing diffuse gastric carcinoma and lobular breast cancer. Not all hereditary diffuse gastric cancer patients have CDH1 gene mutation, suggesting that the other genes may also be involved. In fact, CDH1 mutation is rare in Korea among the patients fulfilling the criteria of hereditary diffuse gastric cancer [23].

The gastric adenomas, either papillary or tubular adenomas, are recognized as premalignant lesions. Unlike colonic adenocarcinomas, which originate predominantly from adenoma, only minor portions of gastric cancers develop from adenomas. Low-grade adenoma is similar to the histology of low-grade colonic adenoma, and high-grade adenomas are characterized by cellular atypia or pronounced architectural disarray encompassing in situ adenocarcinomas. Gastric adenomas can be also divided by gastric, intestinal, mixed, and unclassified using mucin expression, and gastric type adenoma is characterized by biologic aggressiveness and represents the putative precursor lesion of gastric type adenocarcinoma [24].

Molecular Classification

A recent TCGA (The Cancer Genome Atlas) study performing the comprehensive molecular profiling of gastric cancer identified four different molecular subtypes: tumors positive for Epstein–Barr virus (EBV), microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability [25].

EBV-associated gastric cancer has been shown to comprise about 5–10% of gastric cancers around the world. Histologically, gastric cancer with lymphoid stroma is characterized by EBV association, but not all EBV-associated gastric cancer shows the typical histology. EBV-associated gastric cancer is predominated by the male population, and common in stump cancer occurring in anastomosis sites. Epigenetic alterations, particularly DNA methylation of the promoter regions of tumor suppressor genes, were demonstrated frequently in EBV-associated gastric cancer. In fact, EBV-associated gastric cancer is known to show the highest frequency of global hypermethylation among various cancers. The mechanism for the extraordinary hypermethylation is probably host reaction to viral infection. This subgroup has a strong signature of interleukin 12 signaling event, which reflects abundant immune cell infiltration. TCGA study identified the critical association with signal pathways such as PI3K/Akt and JAK2, as well as elevated PD-L1 and PD-L2 expression in the EBV subtype. ARID1A mutation was detected in 10% of gastric cancers, and is most frequent in EBV-associated gastric cancer.

MSI (microsatellite instability) is a genetic alteration caused by inactivation of DNA mismatch repair (MMR) genes. TCGA study identified that patients with microsatellite unstable cancers were relatively older and tended to be female. Microsatellite unstable cancers (MSI gastric cancer) have mostly intestinal histology, and show good prognosis and low recurrence rate. They often show an aberrant epigenetic pattern and MLH1 methylation is a key biomarker in this subtype. MSI gastric cancer frequently shows activation of EGFR-MAPK and PI3K pathways. It shows the highest mutation burden, and consequently elevated mutation rates of various genes including PIK3CA, ERBB3, ERBB2, and EGFR are noted, but amplifications of these genes are not recognized in this subtype. KRAS mutation and BRAF mutation rates are extremely low in gastric cancer; however, the prevalence of KRAS mutation is found most frequently in MSI gastric cancer. Hierarchical clustering of samples and pathways in TCGA study revealed several notable patterns such as elevated expression of mitotic network components.

Removing the EBV-positive or MSI groups, one of the remaining groups was distinguished by the absence of extensive somatic copy-number aberrations into a genomically stable (GS) subtype, in which the diffuse histologic subtype was enriched. RHOA and CDH1 mutations and CLDN18-ARHGAP6 or -ARHGAP26 fusions were frequent in the GS subtype. Those genetic alterations are responsible for the poorly cohesive morphology, resistance to anoikis, and epithelial–mesenchymal transition of the carcinoma cells. Hierarchical clustering of samples and pathways in TCGA study revealed that the GS subtype exhibited elevated expression of cell adhesion pathways.

The other remaining group—except EBV, MSI, and GS subgroups—was distinguished by the degree of aneuploidy into a chromosomally unstable tumor subgroup or chromosomal instability (CIN) subgroup. CIN gastric cancer is characterized by intestinal histology and frequent p53 mutation (71% in TCGA). Each subtype was found throughout the stomach, but CIN subtype was more often noted in the EG junction and cardia. In the CIN subtype, many molecules were confirmed as emerging targets for treatment, such as HER2, EGFR, VEGFR, c-MET, and FGFR2. HER2 is the only validated biomarker in gastric cancer so far, and trastuzumab received regulatory approval as the first targeted drug

for the treatment of advanced HER2-positive gastric cancer. Moreover, CIN subtype has been shown to correlate with intestinal histologic type, consistent with a previous report regarding the relationship between HER2 and intestinal gastric cancer. Activation of tyrosine kinase receptors resulting from amplification or overexpression leading to proliferation and antiapoptotic signals may be a new therapeutic target in CIN gastric cancer. In fact, a genomic study using high-resolution single nucleotide polymorphism (SNP) array revealed that 37% of gastric cancers showed amplification of genes involving RTK/RAS signaling (FGFR2, KRAS, ERBB2, EGFR, and MET) [26]. Because RTK amplification is a potentially druggable alteration, the predictive value of those alterations should be validated. However, amplification of FGFR2 gene or MET genes is shown to be heterogeneous in most cases, and only small numbers of gastric cancer are homogeneously amplified [27]. Therefore, it is questionable whether most of the amplified cases are addicted to those oncogenes or not.

A whole-genome sequencing study revealed the previously well-known mutations such as TP53 mutation in CIN cancers, ARID1A mutation in EBV cancers, and CDH1 mutation in GS cancers, and additional driver mutation of MUC6, CTNNA2, GLI3, RNF43, etc. [28]. However, the prognostic significance of mutation of an individual gene is not well characterized. In contrast, a genome-wide DNA methylation profile revealed that alteration of methylation of GFRA1, SRF, and ZNF382 genes is associated with metastasis and overall survival. It is suggested that the thorough sequencing of gastric cancer may not be sufficient to characterize or classify gastric cancer for clinical purpose.

Cristescu classified Asian gastric cancer into four groups using principal component analysis: MSI, MSS/EMT, MSS/TP53+, and MSS/TP53− [29]. The MSI group overlaps with that in TCGA classification, and the MSS/EMT group includes most of the genomically stable (GS) tumors in TCGA. This ACRG classification is well correlated with the prognosis that the MSI group showed the best outcome, and the MSS/EMT group showed the worst outcome. The clinical significance is validated in other cohorts, such as TCGA or Singapore data. In spite of the introduction of several molecular classifications using whole-genome scale data, translation of this information into daily clinical practice is still very slow. Integration of knowledge from diverse disciplines with high-throughput data might be needed to achieve the successful molecular typing for the clinical application.

Diagnosis, Preoperative Evaluation, and Screening

Gastric cancer has diverse symptoms according to the severity of the disease. The patient is usually asymptomatic in the early stage, but can have various symptoms such as indigestion, epigastric pain, nausea, and vomiting in the advanced stage. Although melena, hematemesis, epigastric mass, and weight loss also can be presented, the symptoms are not specific for the diagnosis of gastric cancer.

Upper gastrointestinal endoscopy is the first choice of modality for the diagnosis of gastric cancer in suspicious cases. Histopathologic evaluation with a biopsy is mandatory for the confirmation of gastric cancer in a suspicious case. The irregular mucosal erosion, ulcer, and nodular change are the main endoscopic findings of early gastric cancer. The abnormal changes of converging folds in gastric cancer include abrupt cutting, clubbing, fusion, and dam formation. Mass formation, decreased distensibility, irregular deep ulcer, and diffuse fold thickening are the hallmarks of advanced gastric cancer (AGC). If the initial biopsy does not reveal the evidence of malignancy in suspicious cases for cancer, re-biopsy is mandatory for the histologic confirmation.

Upper radiographic study with double-contrast using barium is also useful for screening of gastric cancer. In cases of suspicious malignancy, histopathologic confirmation is indispensable by biopsy using endoscopy.

After confirmation of cancer by histopathology, staging workup is mandatory. Current standard staging modalities include abdomen computerized tomography (CT), endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT.

CT has become a representative imaging tool for the staging of gastric cancer, and showed increased diagnostic accuracy of the tumor (T) and node (N) staging with 3-dimensional (3D) reconstruction and isotropic volumetric imaging [30]. EUS can be useful for the evaluation of the depth of tumor invasion (T staging), and may give additional information whether the lesion can be a candidate for endoscopic resection in the early stage. However, EUS did not substantially impact on pretreatment T staging for early gastric cancer compared with conventional white light endoscopy, and may not be routinely necessary to decide the modality of curative resection [31].

PET/CT can be useful to detect unexpected distant metastasis, but is not recommended routinely for limited sensitivity [32]. MRI can be useful for the differential diagnosis of suspicious metastatic lesions in the liver [33].

Population-based screening of gastric cancer has been performed in Korea and Japan where the prevalence of gastric cancer is high. Upper endoscopy or barium study has been the main modality for cancer screening, which has the advantage of early detection of cancer in the area where the prevalence of the disease is high. Sensitivity and specificity of mass screening was 96% and 85% in endoscopy, and 89% and 86% in barium study, respectively [34, 35]. In Korea and Japan, the proportion of early-stage cases is more than 50% at the time of diagnosis of gastric cancer with widespread cancer screening. The screening interval is recommended every 2 years for ages 40–74 in Korea [36].

Endoscopic Treatment of Early Gastric Cancer

Endoscopic resection has been a curative modality for early gastric cancer (EGC) in indicated cases with negligible risk of metastasis. Since endoscopic resection has just started for polypoid-type EGC, endoscopic submucosal dissection (ESD) has become a standard modality for endoscopic resection for EGC with progress of endoscopic accessories and techniques. ESD enables the complete en-bloc resection irrespective of tumor size, shape, or location. The most important advantage of ESD is to preserve the normal function of the stomach with the maintenance of the quality of life without the sacrifice of survival.

Conventional indications for endoscopic resection for EGC in the era before the development of ESD were: (1) differentiated adenocarcinoma confined to the mucosa, (2) elevated type ≤ 2 cm, and (3) depressed type without ulcer ≤ 1 cm because the complete resection was not possible beyond conventional indication [37]. As the complete en-bloc resection has been possible in most cases by ESD, the indication has been expanded by the risk of lymph node metastasis. By the risk factors of lymph node metastasis such as tumor size, differentiation, depth of tumor invasion, and lymphovascular tumor invasion, the current expanded criteria of endoscopic resection of EGC with negligible risk of lymph node metastasis have been proposed as follows: (1) differentiated mucosal cancer without ulcer irrespective of size, (2) differentiated mucosal cancer with ulcer ≤ 3 cm, (3) undifferentiated mucosal cancer ≤ 2 cm, and (4) differentiated submucosal cancer ≤ 500 μ(mu)m depth of tumor invasion (sm1) ≤ 3 cm in size without lymphovascular invasion [38]. The expanded criteria are not the indications by pretreatment diagnosis, but the pathologic criteria of curative resection with negligible risk of lymph node metastasis by the mapping result after ESD.

Complete resection should be confirmed with the histopathologic mapping. If the final result of mapping shows negative tumor margins within the expanded criteria, it can be considered to achieve complete resection. If the tumor margin shows the positive result within the expanded criteria, residual tumor may exist around the resected margin of the stomach. However, residual tumor does not always exist even with incomplete resection because of a false-positive result of mapping or cautery effect that ablates residual tumor around the margin of the stomach [39]. As there can be no residual tumor in spite of incomplete resection in the mapping, close endoscopic follow-up rather than immediate additional resection is recommended for the detection of residual tumor. The additional endoscopic or surgical resection is inevitable for the case of residual tumor during follow-up.

If the final mapping shows the lesion beyond expanded criteria irrespective of tumor margin, the risk of lymph node metastasis cannot be neglected. Therefore, additional surgical resection with regional lymph node dissection is needed in cases beyond expanded criteria irrespective of complete resection.

Regular follow-up is needed after complete resection to detect synchronous or metachronous tumor development. The rate of synchronous and metachronous tumor development is about 5% during 3-year follow-up [40]. The risk factors of synchronous or metachronous tumor development were absence of *H. pylori*, lower third location, mucosal atrophy, and intestinal metaplasia. It has been a controversy whether *H. pylori* eradication could reduce metachronous tumor development after endoscopic resection of early gastric cancer [41, 42].

Complete resection was achieved in 96.1% for conventional indication and 92.5% for expanded criteria [43]. Lymph node metastasis has developed in 0.6% of cases during long-term follow-up. Five-year survival after endoscopic resection of early gastric cancer was 96.6% for conventional indication and 94.2% for expanded criteria, and disease-free survival rate was 100% and 99.3%, respectively, which showed favorable long-term clinical outcomes and was not inferior to those after surgical resection.

Surgery

Lymphadenectomy

One of the important issues for gastric cancer surgery in the 1970s and 1980s was the extent of lymph node dissection. The role of adjuvant chemotherapy after radical gastrectomy predominated in the 1990s, followed by so-called minimal access surgery in the 2000s. Regarding lymphadenectomy, there have been historical differences of opinion about the extent of lymphadenectomy between the East and the West. In the East, radical gastrectomy with extensive lymphadenectomy (D2 lymph node dissection, Fig. 5.1a, b) is considered as the standard of care for most operable gastric cancers [44].

As presented in lymph node (LN) metastasis data from Seoul National University Hospital (SNUH), the probability of LN metastasis increases according to T stage (Fig. 5.2). As the depth of invasion increases, lymph node metastasis expands from N1 area to N2 (defined by Japanese classification of gastric carcinoma) [45]. These data would explain that if only D1 dissection is done for regionally advanced gastric cancer, there will be high local recurrence and can be benefited by radiotherapy and that is why local recurrence is very low in Korea or Japan where D2 dissection even without additional radiotherapy is common practice.

To compare the effectiveness of D1 and D2 lymphadenectomy, a few randomized clinical trials (RCTs) were conducted. Among them, the MRC and Dutch trials showed significantly higher morbidity and mortality, and similar

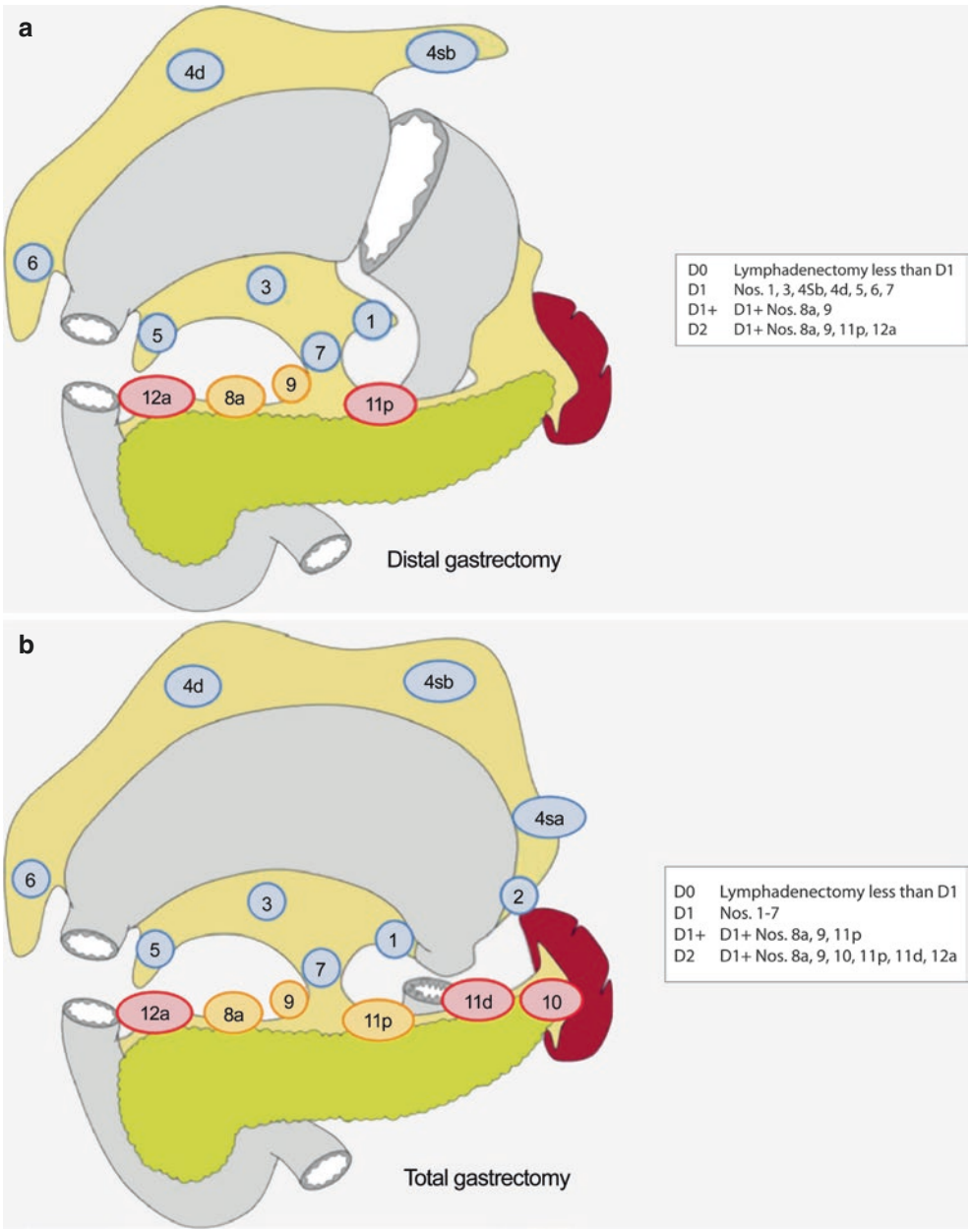


Fig. 5.1 Extent lymph node dissection for gastric cancer (JGCA guideline 2011). (**a**) Distal gastrectomy. (**b**) Total gastrectomy

5-year survival rates after D2 lymphadenectomy [46, 47]. However, these outcomes were significantly worse than those from previous Eastern institutes that believed in the role of D2 lymphadenectomy. In addition, a recently conducted randomized clinical trial from Italy described that D2 lymph node dissection could be a better treatment choice for advanced gastric cancer [48]. Recent systemic review analyzing long-term survival differences after gastrectomy in randomized clinical trials reported association between gastrectomy performed in the East, improved 5-year survival (pooled odds ratio 4.83, 95% C.I. 3.27–7.12) and reduced cancer recurrence (pooled OR 0.33, 95% C.I. 0.2–0.54) even after adjustment for confounding factors [49]. This study suggested that the difference of surgical principle or strategy between the East and West could be a potential explanation for such prognostic discrepancy. In addition, the Dutch trial group finally reported their long-term results that D2 lymphadenectomy is associated with lower locoregional recurrence and gastric cancer-related deaths than D1 lymphadenectomy [50]. Also, according to the final comments from a principal investigator of the MRC trial, suggestion for D1 gastrectomy instead of D2 reflects the failure of the Western surgical community and the results of the MRC trial are no longer a sustainable argument against D2 gastrectomy in modern surgery for invasive gastric cancer [51].

It is important not only to do proper D2 lymphadenectomy for advanced gastric cancer, but it is also important to

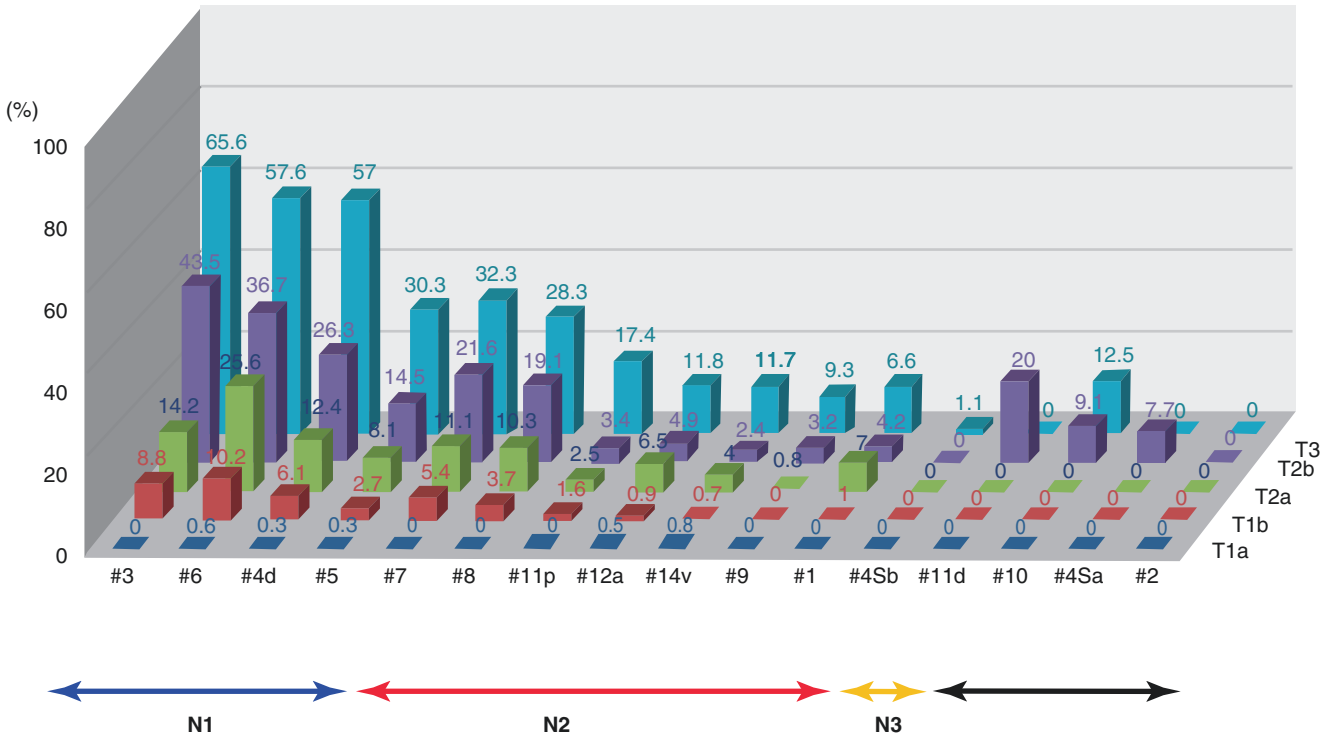


Fig. 5.2 Lymph node (LN) metastasis according to LN station and tumor (T) stage (lower third)

evaluate the metastasis status of the resected lymph nodes in the surgical specimen. A previous study reported that optimal staging after D2 lymph node dissection combined with surgical ex vivo dissection resulted in all patients with >16 examined lymph nodes, and the D2 LN dissection group showed significant better overall survival than the D1 LN dissection group [52]. These differences in the extent of lymph node dissection in patients and ex vivo dissection of specimens may cause different outcomes of gastric cancer patients between the East and the West. According to the seventh AJCC TNM classification, 5-year survival rate at each stage among Korea [53], Japan [54], the United States (SEER data 1973–2005 diagnosed in 1991–2000), and China [55] is as follows: 95.1%, 94.2%, 70.8%, 88.5% for stage Ia, 84.0%, 80.8%, 45.5%, 71.5% for stage IIa, 71.7%, 69.6%, 32.8%, 66.8% for stage IIb. Especially for stage IIIa, the 5-year survival rate in Korea is 58.4%, whereas SEER data show 19.8%.

Table 5.1 Randomized clinical trials comparing laparoscopic-assisted distal gastrectomy (LADG) and open distal gastrectomy (ODG) in early gastric cancer

	LADG		ODG	
	Morbidity	Mortality	Morbidity	Mortality
Kitano et al.	**14.3%** (2/14)	**00.0%** (0/14)	**28.6%** (4/14)	**0.0%** (0/14)
Huscher et al.	**26.7%** (8/30)	**03.3%** (1/30)	**31.0%** (9/29)	**6.9%** (2/29)
Hayashi et al.	**14.3%** (2/14)	**14.3%** (2/14)	**42.9%** (6/14)	**0.0%** (0/14)
JH Lee et al.	**12.5%** (3/24)	**00.0%** (0/24)	**43.5%** (10/23)	**0.0%** (0/23)
YW Kim et al.	**00.0%** (0/82)	**00.0%** (0/82)	**04.9%** (4/82)	**0.0%** (0/82)
HH Kim et al.	**09.5%** (17/179)	**01.1%** (2/179)	**14.9%** (24/161)	**0.0%** (0/161)

Minimal Access Surgery

Laparoscopic gastrectomy for gastric cancer was first reported in 1994 and rapidly adopted in Japan and Korea—in both countries early gastric cancer is dominant [56]. The advantages of minimally invasive surgery have been known as less operative pain, better cosmesis, less inflammatory reaction, rapid recovery of bowel function, shorter hospital stay or rapid return to social activity. To prove operative and oncologic safety, several randomized clinical trials compared the outcome between laparoscopic-assisted distal gastrectomy (LADG) and open distal gastrectomy (ODG) (Table 5.1). The Korean Laparoscopic Gastrointestinal Surgery Study Group (KLASS) conducted a large-scale multi-institutional prospective randomized controlled trial (KLASS-01) for early-stage cancer to compare laparoscopic gastrectomy and open gastrectomy. In the KLASS-01 trial,

Table 5.2 Randomized clinical trial comparing laparoscopic-assisted distal gastrectomy (LADG) and open distal gastrectomy (ODG) in advanced gastric cancer

	Morbidity		Mortality		Survival	
	LADG	ODG	LADG	ODG	LADG	ODG
Ziqiang et al. (China)	13.6% (6/44)	20.7% (12/58)	0%	3.4% (2/58)		
Huscher et al. (Italy)	23% (23/100)		6% (6/100)		59% (5 years)	
H Hur et al. (Korea)	15.4% (4/26)	16.0% (4/25)	0	0	88.2% (3-year overall)	77.2% (3-year overall)
SI Hwang et al. (Korea)	15.6% (7/45)	12.0% (10/83)	2.2% (1/45)	1.2% (1/83)		
J Shuang et al. (China)	5.7% (2/35)	8.6% (3/35)	.	.	Median 36.5 months	Median 38.5 months
A Hamabe et al. (Japan)	24.2% (16/66)	22.8% (23/101)	.	.	89.6% (5-year RFS)	75.8% (5-year RFS)
AC Gordon et al. (Japan)	13.6% (9/66)	25.0% (31/32)	0%	0%	68.6%(IIIa) 65.0% (IIb)	70.5% (IIIa) 67.7% (IIb)

RFS recurrence-free survival

Table 5.3 Nationwide multicenter randomized clinical trials comparing laparoscopic-assisted distal gastrectomy (LADG) and open distal gastrectomy (ODG) in the East

	cStage I		AGC		
	KLASS 01 (NCT00452751)	JCOG 0912	KLASS 02 (NCT01456598)	JLSSG 0901	CLASS 01 (NCT01609309)
Phase	III	III	III	II/III	III
Comparison	LADG vs. ODG	LADG vs. ODG	LADG vs. ODG	LADG vs. ODG	LADG vs. ODG
Inclusion criteria	cStage I	cStage I	cT2/T3/T4a cN0-1	cT2/T3/T4a cN0-2	cT2/T3/T4a cN0-3
Sample size	1400	920	1050	500	1056
Enrollment period	2006–2010	2010-	2011-	2010-	2012-
Primary endpoint	5-year DFS	5-year OS	3-year DFS	*II*: anastomosis leakage or pancreas fistula *III*: RFS	3-year DFS

KLASS Korean Laparoscopic Gastrointestinal Surgery Study Group, *JCOG* Japan Clinical Oncology Group, *JLSSG* Japanese Laparoscopic Surgery Study Group, *CLASS* Chinese Laparoscopic Gastrointestinal Surgery Study Group, *DFS* disease-free survival, *OS* overall survival, *RFS* recurrence-free survival

the overall complication rate was significantly lower in laparoscopic gastrectomy than in open gastrectomy (13.0% vs. 19.9%, $P = 0.001$) [57, 58].

For stage II or III advanced cancer, laparoscopic gastrectomy with D2 lymph node dissection is required, which is a technically demanding and time-consuming procedure. LADG for AGC has been performed by a few institutes, and reported as 11.3–23.0% of morbidity and 0.8–6.0% of mortality (Table 5.2).

The KLASS group reported long-term, large-scale, case-controlled, and case-matched results of laparoscopic gastrectomy for gastric cancer [59]. According to these data, the 5-year survival rate of each stage II and III between LADG and ODG was not significantly different. Based on this promising retrospective experience, several nationwide multicenter phase III randomized clinical trials have been launched (Table 5.3). Among them, KLASS 02 and CLASS 01 finished their patient enrollment in 2015. These randomized clinical trials (RCTs)—including KLASS, CLASS, and Japanese—will provide level 1 evidence for the long-term oncologic outcome of laparoscopic gastrectomy for gastric cancer.

Reduction Surgery

For stage IV gastric cancer, the role of reduction surgery for M1 gastric cancer has been controversial. A few retrospective studies from the East suggested possible survival benefit of gastrectomy in patients with minimal non-curable factors. To evaluate the survival benefit and safety of gastrectomy plus chemotherapy compared to chemotherapy alone in clinical stage IV gastric cancer with a single non-curable factor, an international intergroup study was performed among the Japan Clinical Oncology Group (JCOG), the Korean Gastric Cancer Association (KGCA), and NUSH (REGATTA trial). The primary endpoint was overall survival. The planned sample size was 300 patients in total. Between February 2008 and August 2013, 175 patients (95 in Japan and 80 in Korea) were randomized. The 2-year survival rate was 25.7% (95% CI = 15.7–

36.9%) with gastrectomy plus chemotherapy and 31.4% (95% CI = 20.4–42.9%) with chemotherapy alone, at which point the JCOG Data and Safety Monitoring Committee (DSMC) recommended early termination of the trial based on the overall futile effect. This study concluded that gastrectomy followed by chemotherapy has no survival benefit over chemotherapy alone for AGC patients with a single non-curable factor. Gastrectomy was safely performed with no mortality but associated with an increase of late adverse events and morbidities. Gastrectomy was associated with more frequent and severe chemotherapy-related adverse effects, especially for U lesion or total gastrectomy. Because of a tendency for overall survival benefit in distal gastric cancer, a second study only in patients with distal gastric cancer can be considered.

Peritoneal recurrence, one of the most common findings in stage IV gastric cancer, is considered due to implantation of free intraperitoneal cancer cells exfoliated from the tumor before and during primary surgery. A previous study using ex vivo washing samples of resected stomach with gastric cancer revealed that free cancer cells can be released from the gastric lumen or lymphovascular pedicles opened during gastric cancer surgery, especially in advanced-stage disease [60]. Another clinical observational study also demonstrated that extensive intraoperative peritoneal lavage (EIPL) followed by intraperitoneal chemotherapy (IPC) significantly improved the 5-year survival rate of advanced gastric cancer patients with intraperitoneal free cancer cells without overt peritoneal metastasis (43.8% for EIPL-IPC, 4.6% for IPC, 0% for surgery alone, $P < 0.0001$) [61]. Based on this experience, a randomized clinical trial evaluating survival outcomes after curative gastrectomy between an EIPL group and standard lavage group is ongoing (EXPEL trial, NCT02140024). The planned sample size is 800 in total, and the primary endpoint is 3-year overall survival.

Function Preserving Surgery

Pylorus-preserving gastrectomy (PPG), which was initially introduced for benign peptic gastric ulcers, has been used as an optional treatment for middle-third early gastric cancer (EGC) [62]. PPG has been known to have functional advantages including nutritional benefit, lower incidence of dumping syndrome, bile reflux, or gallstone formation [63–65]. According to the Japanese gastric cancer treatment guidelines revised in 2010, PPG can be used for cT1cN0 gastric cancer in the middle portion of the stomach with the distal tumor border at least 4 cm proximal to the pylorus1. In terms of lymph node metastasis and survival, several retrospective studies showed that laparoscopy-assisted PPG (LAPPG) could be a safe operation with satisfactory postoperative long-term outcomes (overall 3YSR = 97.8% and disease-specific 3YSR = 99.3%) [66–68]. In order to prove the advantage of LAPPG for middle-third early gastric cancer, the KLASS-04 trial comparing the quality of life between LAPPG and LADG has been started in 2015. The planned sample size is a total of 256, and the primary endpoint is the incidence of dumping syndrome, assessed by Sigstad score at postoperative 1 year [69].

Robotic Surgery

Robot-assisted surgery is a laparoscopic surgery using articulating robotic instruments. Compared to conventional laparoscopic surgery, robotic surgery has some benefits such as increased degree of freedom of robotic arms, scaled maneuver of the instruments, a steady camera platform, and filtration of resting tremor of surgeon's hand. Several reports about robotic surgery for gastric cancer suggest comparable short-term morbidity and oncologic outcomes compared with laparoscopic gastrectomy [70, 71]. However, the concrete advantage of robotic surgery for the patient still remains elusive in terms of the similar number of trocars, longer operation time, negligible difference in blood loss, similar surgical stress, and much higher cost [72, 73]. To investigate the role of robotic gastrectomy for gastric cancer, the Korean Robot Gastrectomy Study Group conducted a multicenter retrospective and prospective, case-matched clinical trial comparing robotic versus laparoscopic gastrectomy for EGC from 2010. Enrollment of 400 patients (200 in each group) was finished in 2012. This trial reported their short-term outcome in 2015 that robotic gastrectomy is not superior to laparoscopic gastrectomy in terms of perioperative surgical outcomes including morbidity, mortality, blood loss, and length of hospital stay, in spite of significantly longer operation time and higher total cost compared to laparoscopic gastrectomy [74]. But as technologies are developing rapidly, new devices are coming to take advantage of robot technology, and evaluation through clinical trials is undergoing.

Systemic Treatment

Adjuvant Treatment

In order to improve the cure rate of resectable gastric cancer, several treatment strategies have been evaluated. These include postoperative or adjuvant chemotherapy, adjuvant chemoradiotherapy, and perioperative chemotherapy [75].

Adjuvant Chemoradiotherapy

Chemoradiotherapy after surgery was tested in three phase III trials. Two studies compared chemoradiotherapy with surgery alone and the other compared chemoradiotherapy with adjuvant chemotherapy.

The Intergroup 0116 (SWOG9008/INT0116) trial enrolled 559 gastric cancer patients with ≥ T3 and/or node-positive patients who received R0 surgery and randomized to observation (n = 227) or chemoradiotherapy (n = 282) [76]. In the chemoradiotherapy arm, fluorouracil (FU) and leucovorin were administered before, during, and after radiation (4500 cGy). According to 10-year follow-up data, overall survival and relapse-free survival are continuously benefited by chemoradiotherapy compared to observation [77]. Overall survival was 35 months and 27 months, respectively (hazard ratio [HR]: 1.32; 95% confidence interval [CI] 1.10–1.60; P = 0.0046) and relapse-free survival was 27 months and 19 months, respectively (HR: 1.51; 95% CI 1.25–1.83; $P < 0.001$). Among the enrolled patients, D2 surgery was performed in only 10% of the population. More than 50% of patients received D0 resection and 36% received D1 resection. The locoregional relapse was reduced from 47% in the observation arm to 24% in the radiotherapy arm. This study suggests the radiotherapy might compensate for inadequate surgery.

The CALGB80101 trial was conducted after following the scheme of INT0116 [78]. This trial used adjuvant chemoradiotherapy with FL (5-FU/leucovorin) as the reference arm and investigated the efficacy of chemoradiotherapy with ECF (epirubicin + cisplatin +5-FU)—1 cycle of ECF (E 50 mg/m^2 on day 1, C 60 mg/m^2 on day 1, and 5-FU 200 mg/m^2/day CI on days 1–21) followed by 45 Gy (1.8 Gy/day) and concurrent 5-FU (200 mg/m^2/day CI throughout RT), followed by 2 cycles of a reduced dose of ECF (E 40 mg/m^2 on day 1, C 50 mg/m^2 on day 1, and 5-FU 200 mg/m^2/day CI on days 1–21). The overall survival of the FL arm and the ECF arm were similar (37 months and 38 months, respectively; HR: 1.03; 95% CI: 0.80–1.34; P = 0.80). Thus, this study suggests that the intensification of chemotherapy during adjuvant radiotherapy might not be beneficial. Furthermore, the administration of 3 cycles of ECF is inadequate to alter the outcomes.

The role of adjuvant chemoradiotherapy after D2 surgery was explored in the Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial [79]. In this study, the reference arm was not surgery alone, but adjuvant chemotherapy (capecitabine + cisplatin 6 cycles). A total of 458 patients were randomized to the adjuvant chemotherapy arm or the adjuvant chemoradiotherapy arm (capecitabine + cisplatin for 2 cycles followed by capecitabine during radiotherapy, then capecitabine + cisplatin for 2 cycles). The majority (75%) of the adjuvant chemotherapy arm and 82% of the adjuvant chemoradiotherapy arm completed the scheduled treatment. The 3-year disease-free survival rate, the primary endpoint of the study, was 78% in the adjuvant chemotherapy arm and 74% in adjuvant chemoradiotherapy arm (P = 0.0862). After 7-year follow-up, the overall survival (HR 1.130, P = 0.5272) and disease-free survival (HR 0.740, P = 0.0922) were similar between two arms [80]. Therefore, the addition of radiotherapy to adjuvant chemotherapy might not be beneficial after D2 surgery.

Perioperative or Neoadjuvant Chemotherapy

In the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, 503 patients with gastric cancer, gastroesophageal junction cancer, or esophageal cancer were randomized to the surgery alone or the perioperative chemotherapy [81]. The perioperative chemotherapy arm received three preoperative cycles of ECF (epirubicin + cisplatin + 5-FU) and three postoperative cycles of ECF. The 5-year survival rate was 23% and 36% in the surgery-alone arm and the perioperative chemotherapy arm, respectively (HR: 0.75; 95% CI: 0.60–0.93; P = 0.0009). In this trial, approximately 25% of enrolled patients had esophageal or gastroesophageal junction cancers, and 26.5% of the patients underwent an esophagectomy. D2 surgery was performed on 68% of patients [82].

In the Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC) and Fédération Francophone de Cancérologie Digestive (FFCD) trial, 224 patients with resectable adenocarcinoma of stomach, gastroesophageal junction, and lower esophagus were randomized to the surgery alone or the perioperative chemotherapy (5-FU + cisplatin, total 6 cycles) [83]. The 5-year survival rate was 38% in the chemotherapy arm and 24% in the surgery-alone arm (HR: 0.69; 95% CI: 0.50–0.95; P = 0.02). Approximately 50% of the patients received transthoracic or transhiatal esophagectomy.

Adjuvant Chemotherapy

The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) enrolled 1059 patients with stage II or III (based on Japanese staging system) gastric cancer after D2 resection [84]. The used adjuvant chemotherapy was S-1 (tegafur, gimeracil, and oteracil, 80 to 120 mg per day) with 4 weeks/2 weeks on/off schedule for 12 months. After 5 years of follow-up, the overall survival rate at 5 years was higher in the S-1 arm (71.7%) than that of the surgery-alone arm (61.1%) (HR: 0.669; 95% CI: 0.540–0.828) [85]. However, in the subgroup analysis of ACTS-GC, the benefit of adjuvant S-1 was compromised in stage IIIB (HR: 0.855; 95% CI: 0.510–1.431) and stage IV (HR: 0.784; 95% CI: 0.422–1.458) based on the UICC 6th staging system. Therefore, this study suggested further investigation was indicated in order to improve the prognosis of this population.

The Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial investigated the benefit of combination chemotherapy of XELOX (capecitabine and oxaliplatin) compared to surgery alone in stage II or III gastric cancer patients after D2 surgery [86]. The XELOX regimen was composed of capecitabine 2000 mg/m^2/day for 14 days

and oxaliplatin 130 mg/m^2 on day 1, which was repeated every 3 weeks for 8 cycles. After 34 months of follow-up, the 3-year disease-free survival (the primary endpoint) was 74% in the XELOX arm and 59% in the surgery-alone arm (HR: 0.56; 95% CI: 0.44–0.72; $P < 0.0001$). Furthermore, these benefits were observed across all stages; the HRs for disease-free survival were 0.55 (95% CI: 0.36–0.84), 0.57 (95% CI: 0.39–0.82), and 0.57 (95% CI: 0.35–0.95) in stage II, IIIA, and IIIB, respectively. After 5-year follow-up, 5-year disease-free survival was 68% (95% CI 63–73) in the XELOX arm versus 53% (47–58) in the surgery-alone arm. Estimated 5-year overall survival was 78% (95% CI 74–82) in the XELOX arm versus 69% (64–73) in the surgery-alone arm [87].

Taken together, gastric cancer patients who received D2 curative resection or good quality surgery get the definite survival benefit by postoperative adjuvant chemotherapy.

Palliative Chemotherapy

Cytotoxic Chemotherapy

Palliative cytotoxic chemotherapy has shown the survival benefit compared with best supportive care in unresectable advanced gastric cancer patients [88]. Analysis of chemotherapy versus best supportive care (HR = 0.39; 95% CI, 0.28–0.52) and combination versus single agent, mainly fluorouracil-based chemotherapy (HR = 0.83; 95% CI = 0.74–0.93), showed significant overall survival benefits in favor of chemotherapy and combination chemotherapy, respectively. With the introduction of new agents—including capecitabine, S-1, paclitaxel, docetaxel, and irinotecan—to improve the overall survival of gastric cancer patients, various regimens have been tested in phase III studies.

The V325 phase III study compared the DCF (docetaxel, cisplatin, 5-FU) with CF (cisplatin, 5-FU) as first-line therapy for advanced gastric cancer [89]. A total of 455 patients were enrolled and the overall survival was longer in the DCF arm (9.2 months vs 8.6 months, HR 0.77, $P = 0.02$). However, grade 3/4 adverse events occurred more frequently in the DCF arm (69% vs 59%). Grade 3/4 neutropenia (82% vs 57%), diarrhea (19% vs 8%), lethargy (19% vs 14%), and complicated neutropenia (29% vs 12%) were more common in the DCF arm. Therefore, this regimen is not as popular as its original dose and schedule because of toxicity.

Another phase III compared irinotecan/5-FU/leucovorin to 5-FU/cisplatin in chemotherapy-naïve 333 gastric or gastroesophageal junction cancer patients [90]. The overall survival, time to progression, and overall response rates were similar between two arms (9.0 months vs 8.7 months: 5.0 month vs 4.2 months; 31.8% vs 25.8%).

The S-1 Plus Cisplatin versus S-1 in RCT in the Treatment for Stomach Cancer (SPIRITS) study was a phase III trial comparing S-1 monotherapy versus S-1 plus cisplatin as first-line treatment for advanced gastric cancer [91]. A total of 305 patients were enrolled. The overall survival was significantly longer in the S-1/Cisplatin arm (13.0 months vs 11.0 months, HR 0.77, $P = 0.04$) and progression-free survival was also improved in S-1/Cisplatin arm (6.0 months vs 4.0 months, $P < 0.0001$). Grade 3/4 adverse events—including leucopenia, neutropenia, anemia, nausea, and anorexia—were more frequently observed in the combination arm.

The First-Line Advanced Gastric Cancer Study (FLAGS) was a phase III trial to compare S-1/Cispatin with infusional 5-FU/Cisplatin in non-Asian patients [92]. One thousand fifty-three patients were enrolled in this study. The overall survival was similar between two arms (8.6 months vs 7.9 months, HR 0.92, $P = 0.20$). The safety profile favored the S-1/Cisplatin arm. Grade 3/4 neutropenia (32.3% vs 63.6%), complicated neutropenia (5.0% vs 14.4%), stomatitis (1.3% vs 13.6%), and treatment-related death (2.5% vs 4.9%) were all less frequent in the S-1/Cisplatin arm.

The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) study was a 2-by-2 design, randomized trial to compare the capecitabine with infusional 5-FU and oxaliplatin with cisplatin in esophagogastric cancer [93]. A total of 1002 patients were randomized to ECF (epirubicin/cisplatin/5-FU), ECX (epirubicin/cisplatin/capecitabine), EOF (epirubicin/oxaliplatin/5-FU), and EOX (epirubicin/oxaliplatin/capecitabine) arms. For the capecitabine-5-FU comparison, the HR for death in the capecitabine group was 0.86 (95% CI, 0.80–0.99); for the oxaliplatin–cisplatin comparison, the HR for the oxaliplatin group was 0.92 (95% CI, 0.80–1.10). The overall survival in the ECF, ECX, EOF, and EOX groups were 9.9 months, 9.9 months, 9.3 months, and 11.2 months, respectively. Progression-free survival and response rates did not differ significantly among the regimens. Therefore, capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated esophagogastric cancer.

The ML17032 study was a randomized phase III noninferiority trial to compare capecitabine/cisplatin (XP) with 5-FU/cisplatin (FP) as first-line treatment for advanced gastric cancer [94]. A total of 316 patients were enrolled and the primary endpoint was to confirm noninferiority of XP versus FP for progression-free survival. The progression-free survival was 5.6 months and 5.0 months in the XP and FP arms, respectively. The primary endpoint was met with an unadjusted HR of 0.81.

The JCOG9912 study was a randomized phase III trial to compare 5-FU versus irinotecan plus cisplatin versus S-1 in metastatic gastric cancer [95]. The overall survival was 10.8 months, 12.3 months, and 11.4 months in the 5-FU, irinotecan/cisplatin, and S-1 arms, respectively. S-1 was noninferior to 5-FU. The irinotecan and cisplatin combination was not superior to 5-FU.

The French intergroup study was a randomized phase III trial to compare ECX (epirubicin, cisplatin, and capecitabine) with FOLFIRI (fluorouracil, leucovorin, and irinotecan) as first-line treatment for advanced gastric or gastroesophageal junction adenocarcinoma [96]. A total of 416 patients were enrolled. The primary endpoint was a time-to-treatment failure, which was significantly longer with FOLFIRI than with ECX (5.1 vs 4.2 months; $P = 0.008$). There was no significant difference between the 2 groups in progression-free survival (5.3 months v 5.8 months, $P = 0.96$) and overall survival (9.5 months vs 9.7 months, $P = 0.95$). FOLFIRI was better tolerated (overall rate of grade 3/4 toxicity, 69% vs 84%; $P < 0.001$; hematologic adverse events, 38% vs 64.5%; $P < 0.001$). This study suggested that the role of anthracycline in gastric cancer is suspicious.

With those evidence, the two drug combination regimens composed of fluoropyrimidine and platinum are most widely used as first-line treatment of advanced gastric and gastroesophageal junction cancer across the regions.

Second-Line Chemotherapy

The benefit of second-line chemotherapy in advanced gastric cancer has been proven by several phase III studies.

A Korean phase III study compared second-line chemotherapy with best supportive care (BSC) in patients with 1 or 2 prior chemotherapy regimens involving both fluoropyrimidines and platinum [97]. Second-line chemotherapy was chosen by the investigator's discretion between docetaxel and irinotecan. The overall survival was improved by chemotherapy (5.3 months vs 3.8 months, HR 0.657, $P = 0.007$). The adverse events were similar in the chemotherapy arm and the best supportive care arm.

The COUGAR-02 study was a phase III trial to compare the efficacy of docetaxel compared with active symptom control in patients who had progressed on or within 6 months of first-line treatment [98]. A total of 168 patients were enrolled. The overall survival, the primary endpoint, was significantly prolonged by docetaxel (5.2 months vs 3.6 months, HR 0.67, $P = 0.01$). Docetaxel was associated with higher incidence of grade 3/4 neutropenia (15% vs 0%), infection (19% vs 3%), and febrile neutropenia (7% vs 0%). Disease-specific health-related quality of life (HRQoL) measures also showed benefits for docetaxel in reducing dysphagia ($P = 0.02$) and abdominal pain ($P = 0.01$).

Targeted Therapy in Gastric Cancer

HER2

Human epidermal growth factor receptor 2 (HER2) is not infrequently overexpressed or amplified in gastric cancer. In the ToGA (Trastuzumab for Gastric Cancer) trial, tissue specimens from 3807 patients were collected and analyzed at a central laboratory using both immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) methods [99]. HER2 status was defined as positive if IHC 3+ or FISH-positive. The overall HER2 positivity rate was 22.1%. HER2 positivity was more common in gastroesophageal junction cancer than gastric cancer, and in intestinal type than diffuse type [100]. There were no marked racial differences. More recent studies report that HER2 is amplified and/or overexpressed in 11–16% of gastric cancer [101–103].

In HER2-positive gastric cancer, trastuzumab prolonged the overall survival (OS) when combined with cytotoxic chemotherapy in the ToGA trial. The ToGA trial was a randomized multicenter phase III study in HER2-positive gastric cancer. A total of 584 HER2-positive patients were randomized to chemotherapy (5-FU/cisplatin or capecitabine/cisplatin) with or without trastuzumab. The OS, primary endpoint, was significantly prolonged (HR 0.74; 95% CI: 0.60–0.91; $P = 0.0046$), and all other efficacy endpoints including objective response rate and progression-free survival were improved. The benefit of trastuzumab was especially greater in patients with HER2 3+ or HER2 2+/FISH (+) (HR 0.65; 95% CI: 0.51–0.83), and median survival of this group was 16.9 months. This was the first success of a targeted agent in gastric cancer.

Although trastuzumab-based first-line treatment represents the standard approach for HER2-positive gastric cancer, not all patients benefit from this treatment, and the overall response rate (ORR) has been variable (about 32–68%) [104, 105]. This implies that there is a proportion of the patients who are not responsive to trastuzumab, even though their tumors are conventionally defined as HER2-positive gastric cancer.

A recent report suggested that the level of HER2 gene amplification was a predictive factor for sensitivity to trastuzumab-based therapy in advanced gastric cancer [106]. Patients with a HER2/chromosome enumeration probe 17 (CEP17) ratio of more than 4.7 had favorable clinical outcomes. Another study suggested that the cutoff value of HER2/CEP17 ratio for selection of patients with HER2 IHC $\leq$ 2+ to receive trastuzumab treatment would be considered to be 3.69, which is higher than the conventional consensus of 2.0 [107]. Moreover, in patients with IHC 3+, information from HER2 gene amplification might not influence clinical decisions regarding trastuzumab-based treatment. However, in patients with an IHC $\leq$ 2+, further information from HER2 gene amplification status could provide the clinician with better guidance in selecting patients who might benefit from trastuzumab.

Lapatinib, a dual inhibitor of HER1 and HER2 tyrosine kinase, was also tested in gastric cancer. In the TyTan (Tykerb with Taxol in Asian HER2-Positive Gastric Cancer) trial, 261 patients with HER2-amplified gastric cancer for the second-line treatment were randomized to paclitaxel (Taxol) with or without lapatinib (Tykerb) [108]. Even though OS

was better with lapatinib plus paclitaxel in HER2 IHC3+ patients, the addition of lapatinib to paclitaxel did not significantly improve OS in the whole population.

In the LOGiC (Lapatinib Optimization Study in the HER2-Positive Gastric Cancer) trial, 545 patients with HER2-amplified gastric cancer for the first-line treatment were randomized to capecitabine/oxaliplatin with or without lapatinib [109]. The OS was not different between lapatinib and placebo arm (12.2 months vs 10.5 months, HR 0.91; 95% CI: 0.73–1.12) in the whole population. Prespecified subgroup analyses showed significant improvements in OS in Asian patients (HR = 0.68) and those under 60 years (HR = 0.69).

Pertuzumab binds to the dimerization domain (extracellular domain II) of HER2, which leads to blocking of ligand-induced HER2 heterodimerization. The binding site of pertuzumab is different from that of trastuzumab. The combination of trastuzumab and pertuzumab synergistically inhibited tumor growth both in vitro and in vivo [110, 111]. Preclinical studies of a human HER2-positive gastric cancer xenograft model showed enhanced antitumor activity when pertuzumab and trastuzumab were combined, compared with either antibody alone through the potentiation of cell growth inhibition, apoptosis activity, cell killing activity by antibody-dependent cell-mediated cytotoxicity (ADCC), and antiangiogenic activity [112].

The JACOB study, a phase III trial of trastuzumab/capecitabine/cisplatin, with or without pertuzumab in HER2-positive gastric and gastroesophageal junction cancer is ongoing (ClinicalTrials.gov Identifier: NCT01774786). The dose of pertuzumab is 840 mg every 3 weeks based on the JOSHUA study [113]. In this study, HER2-positivity was defined as HER2 IHC3+ or IHC2+/FISH+, and the primary endpoint was OS and the secondary endpoint were progression-free survival (PFS), objective overall response, duration of response, clinical benefit rate, and safety. Patient enrollment of up to 780 patients has been completed.

Overall survival was not significantly different between treatment groups. Median overall survival 17.5 months; 95% CI 16.2–19.3) in the pertuzumab group and 14.2 months; 95% CI 12.9–15.5) in the control group; hazard ratio 0.84; 95% CI 0.71–1.00); P = 0.057). Adding pertuzumab to trastuzumab and chemotherapy did not significantly improve overall survival in patients with HER2-positive metastatic gastric cancer [114].

Trastuzumab emtansine is an antibody–drug conjugate, that is, trastuzumab is linked to DM1. The GATSBY trial is the phase II/III study to evaluate the efficacy and safety of trastuzumab emtansine compared to standard taxane treatment in HER2-positive second-line gastric or gastroesophageal junction cancer patients (ClinicalTrials.gov Identifier: NCT01641939). The primary endpoint is overall survival. Patient enrollment (412 patients) has been completed.

OS was 7.9 months (95% CI 6.7–9.5) with T-DM1 2·4 mg/kg weekly and 8.6 months (7.1–11.2) with taxane treatment (HR 1.15, 95% CI 0.87–1.51, one-sided P = 0.86). T-DM1 was not superior to taxane in 2nd-line patients with previously treated, HER2-positive advanced gastric cancer [115].

VEGFR2

Vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathway is activated in gastric cancer, and lots of evidence has been accumulated that when activated this pathway confers the poor prognosis to gastric cancer patients [116, 117].

Bevacizumab, the antibody against VEGF-A, was tested in the AVAGAST (Avastin for Advanced Gastric Cancer) study [118]. A total of 774 gastric cancer patients for first-line treatment were randomized to capecitabine/cisplatin with or without bevacizumab (Avastin) arms. The primary endpoint was overall survival. Progression-free survival (6.7 months vs 5.3 months, HR 0.80, P = 0.0037) and overall response rate (46.0% vs 37.4%, P = 0.0315) were improved by addition of bevacizumab to the chemotherapy. However, overall survival was not prolonged (12.1 months vs 10.1 months, HR 0.87, P = 0.1002). The benefit by bevacizumab was different according to the geographic regions. The most common grade 3–5 adverse events were neutropenia (35%, bevacizumab vs 37%, placebo), anemia (10% vs 14%), and decreased appetite (8% vs 11%). Another similar designed phase III study, AVATAR trial, also failed to show the improvement of overall survival by bevacizumab in Chinese gastric cancer patients (HR 1.11, P = 0.5567) [119].

Ramucirumab is a direct inhibitor of VEGFR2, where it binds to the extracellular VEGF-binding domain. It thus prevents the binding of the VEGF ligand to the VEGFR2 receptor. Ramucirumab leaves the VEGFR1 receptor alone, which behaves like a decoy receptor, providing additional potency to the VEGFR2 inhibitory effect. VEGFR2 is expressed not only on the endothelial cells but also on macrophages. Inhibition of these macrophages by ramucirumab results in decreased tumor immune infiltration, cytokine and chemokine release, which thereby decrease tumor growth and proliferation.

The REGARD trial (ramucirumab monotherapy for previously treated advanced gastric or gastroesophageal junction adenocarcinoma) was a double-blind, placebo-controlled, phase III study in gastric or gastroesophageal cancer patients who had received the fuoropyrimidine or platinum-based chemotherapy [120]. A total of 355 patients with Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 were enrolled and randomized to ramucirumab or placebo in a 2:1 ratio. The primary endpoint was overall survival. The study population was composed of 76% Caucasian and 15% Asian. The overall survival was prolonged by ramucirumab compared with placebo (5.2 months vs 3.8 months, HR 0.77, P = 0.047).

This absolute overall survival by ramucirumab was comparable to those that can be obtained by cytotoxic chemotherapy in a second-line setting of gastric cancer. The progression-free survival was also improved from 1.3 months to 2.1 months (HR 0.483, $P < 0.0001$). The response rate was similar between the two arms (3% vs 3%); however, the disease control rate was significantly improved in the ramucirumab arm (49% vs 23%). Hypertension was more frequently observed in the ramucirumab arm compared with the placebo arm (all grade 16% vs 8%). However, bleeding (13% vs 11%), arterial thromboembolism (2% vs 0%), venous thromboembolism (4% vs 7%), proteinuria (3% vs 3%), and fistula formation (<1% vs <1%) were reported to be similar between the two arms.

The RAINBOW trial (ramucirumab plus paclitaxel versus placebo plus paclitaxel) was another phase III study using ramucirumab in a second-line setting of gastric or gastroesophageal junction adenocarcinoma patients [121]. A total of 665 patients whose disease showed progression during or within 4 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline were enrolled and randomized to ramucirumab plus paclitaxel or placebo plus paclitaxel in a 1:1 ratio. Asian patients were 33% of the ramucirumab arm and 36% of the placebo arm. The primary outcome was overall survival. Overall survival was significantly increased in the ramucirumab plus paclitaxel group compared with the placebo and paclitaxel group (9.6 months vs 7.4 months, HR 0.807, $P = 0.017$). Progression-free survival was also improved by ramucirumab (4.4 months vs 2.9 months, HR 0.635, $P < 0.0001$). Furthermore, the response rate was also higher in the ramucirumab arm (28% vs 16%, $P = 0.0001$). The incidence of grade 3 or 4 adverse events was higher in the ramucirumab plus paclitaxel group, including grade 3 or 4 neutropenia (41% vs 19%), leucopenia (18% vs 6%), and grade 3 hypertension (14% vs 2%), abdominal pain (6% vs 3%), and fatigue (12% vs 5%).

Now, the clinical trials using ramucirumab in first-line gastric or gastroesophageal cancer setting are ongoing to see the efficacy of ramucirumab on top of standard chemotherapy. (ClinicalTrials.gov Identifier: NCT02314117, NCT02539225).

RAINFALL study tested the role of ramucirumab in the 1st-line setting of advanced gastric cancer. 645 patients were randomly assigned to receive ramucirumab plus fluoropyrimidine and cisplatin ($n = 326$) or placebo plus fluoropyrimidine and cisplatin ($n = 319$). The primary endpoint was investigator-assessed PFS analysed by intention to treat in the first 508 patients. Investigator-assessed PFS was significantly longer in the ramucirumab group than the placebo group (5.7 months vs 5.4 months, HR 0.753, 95% CI 0.607–0.935, $P = 0.0106$). There was no difference in OS between groups (11.2 months vs 10.7 months, HR 0.962, $P = 0.6757$) [122].

Apatinib is a small-molecule VEGFR tyrosine kinase inhibitor. In a randomized phase II study, 144 gastric cancer patients with prior lack of response or intolerance to at least two chemotherapeutic regimens (including both platinum and fluoropyrimidine) were enrolled and randomized to apatinib (850 mg qd or 425 mg bid) or placebo [123]. The progression-free survival, primary endpoint, was improved by apatinib (3.67 months, 850 mg qd; 3.20 months 425 mg bid) versus 1.40 months (HR 0.18, $P < 0.001$, 850 mg qd; HR 0.21, $P < 0.001$, 450 mg bid). Patients treated with apatinib had a significantly better disease control rate (51.06%, 850 mg vs 34.78%, 425 mg bid vs 10.42%, placebo, $P < 0.001$) than those given placebo. Grade 3/4 adverse events that occurred in more than 5% of patients were hand-foot syndrome, hypertension, thrombocytopenia, anemia, elevated aminotransferase and bilirubin levels, and diarrhea. A phase III study of apatinib enrolled 273 Chinese gastric cancer patients who have failed to 2 kinds of chemotherapy and compared the overall survival of apatinib to that of placebo [124]. The overall survival was improved in the apatinib arm (6.5 months vs 4.7 months, HR 0.71, $P < 0.016$).

In a similar way, regorafenib, a multikinase inhibitor that targets VEGFR2, VEGFR1, VEGFR3, fibroblast growth factor receptor 1 (FGFR1), RAF, KIT, RET, and BRAF, improved the progression-free survival of gastric or gastroesophageal junction cancer patients who have failed to more than one chemotherapy compared with placebo in a randomized phase II study (2.6 months vs 0.9 months, HR 0.40, $P < 0.0001$) [125].

EGFR

Epidermal growth factor receptor (EGFR) overexpression occurs in 27–55% of esophagogastric adenocarcinomas, and correlates with poor prognosis [126].

The EXPAND trial (Erbitux in Combination With Xeloda and Cisplatin in Advanced Esophagogastric Cancer) was a randomized, open-label phase III study of capecitabine (Xeloda) and cisplatin with or without cetuximab (Erbitux) [127]. A total of 904 chemotherapy-naïve patients with gastric or gastroesophageal junction cancer were enrolled. There was no patient selection based on any biomarker including EGFR status. The primary endpoint was progression-free survival. Addition of cetuximab to capecitabine/cisplatin provided no additional benefit to chemotherapy alone. Progression-free survival was 4.4 months in the cetuximab arm and 5.6 months in chemotherapy-alone arm (HR 1.09, $P = 0.32$). Overall survival was not improved by cetuximab (9.4 months vs 10.7 months, HR 1.00, $P = 0.95$). Overall response rate and disease control rate were also similar between the two arms. Grade 3/4 skin reaction (13% vs 0%), acne-like rash (11% vs 0%), and mucositis (4% vs 2%) were more frequently observed in the cetuximab arm.

The REAL3 trial was another randomized, open-label phase III study of EGFR-targeting agent, panitumumab [128]. A total of 553 patients were enrolled regardless of

EGFR status, and randomized to EOC (epirubicin, oxaliplatin, capecitabine) chemotherapy with or without panitumumab. In the panitumumab arm, EOC chemotherapy was compromised based on a previous phase I study of a four drug combination: epirubicin 50 mg/m(2) and oxaliplatin 100 mg/m(2) on day 1, capecitabine 1000 mg/m(2) per day on days 1–21 from original EOC: epirubicin 50 mg/m(2) and oxaliplatin 130 mg/m(2) on day 1 and capecitabine 1250 mg/m(2) per day on days 1–21 [129]. The primary endpoint was overall survival. The overall survival of the panitumumab arm was not improved compared with the chemotherapy-alone arm, and showed even worse survival (8.8 months vs 11.3 months, HR 1.37, P = 0.0013). Furthermore, grade 3/4 diarrhea (17% vs 11%), rash (11%, vs 1%), mucositis (5% vs 0%), and hypomagnesemia (5% vs 0%) were more common in the panitumumab arm. Therefore, the addition of panitumumab to EOC chemotherapy does not increase overall survival and cannot be recommended for use in an unselected population with advanced esophagogastric adenocarcinoma.

In a randomized phase II study of nimotuzumab, 83 patients who progressed after previous 5-FU-based therapy were randomly assigned to irinotecan or irinotecan plus nimotuzumab [130]. The overall survival and progression-free survival was not different between the two arms. However, the overall survival of patients with EGFR2+/3+ was 11.9 months in nimotuzumab and 7.6 months in irinotecan monotherapy, respectively. Based on this finding, phase III study of nimotuzumab and irinotecan as second-line in EGFR overexpressed gastric or gastroesophageal junction cancer is ongoing (ClinicalTrials.gov Identifier: NCT01813253).

MET

In gastric cancer, MET is overexpressed in 21.5% (IHC 2+) and 2.3% (IHC 3+) of patients, respectively, and 3.4% of patients showed *MET* gene amplification [131]. Patients with overexpression of MET show worse prognosis. Hepatocyte growth factor (HGF) is the only ligand to the MET receptor. Increased serum concentrations of HGF were associated with disease stage and decreased after resection [132]. Rilotumumab, the antibody against HGF, was tested in a randomized phase II study [133]. A total of 121 unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma patients were randomized to ECX (epirubicin/cisplatin/capecitabine) + placebo, ECX + rilotumumab 15 mg/kg, and ECX + rilotumumab 7.5 mg/kg arm. The progression-free survival, the primary endpoint, was 5.7 months (HR 0.60 vs placebo, P = 0.016) in both rilotumumab arms combined, and 4.2 months in the placebo arm. In the rilotumumab arm, grade 3/4 neutropenia (44% vs 28%), venous thromboembolism (20% vs 10%), and any grade peripheral edema (27% vs 8%) were more frequently observed compared with the placebo arm. According to the analysis based on tumor MET expression levels, in the placebo arm, overall survival was shorter in the MET-positive subgroup than in the MET-negative subgroup (5.7 months vs 11.5 months). Interestingly, in the MET-positive subgroup, overall survival was improved with the addition of rilotumumab (10.6 months vs 5.7 months). In the MET-negative subgroup, overall survival was similar between the combined rilotumumab and placebo arms (11.1 months vs 11.5 months). Based on this finding, RILOMET-1, the phase III study of rilotumumab was conducted [134]. This study enrolled only HER2-negative, MET-positive gastric or gastroesophageal junction cancer patients and randomized to ECX with or without rilotumumab arm to compare the overall survival. A total of 609 patients were enrolled, but the study was stopped early based on an imbalance in deaths. The overall survival was even worse in the rilotumumab arm compared with the placebo arm (9.6 months vs 11.5 months, HR 1.37, P = 0.016). No subgroups seemed to benefit with rilotumumab, including those with higher percentages of cells with ≥1+ MET expression. The most common adverse events that were more frequently observed in the rilotumumab arm were peripheral edema, hypoalbuminemia, deep vein thrombosis, and hypocalcemia.

Onartuzumab is the antibody against MET receptor sema domain. METGastric is the phase III study of onartuzumab in combination with MFOLFOX6 in patients with metastatic HER2-negative and MET-positive gastric or gastroesophageal junction cancer [135]. The study was designed to enroll up to 800 patients and powered to demonstrate the improvement of overall survival from 9 months to 12.3 months (intent to treat [ITT] population; HR 0.73) and 9 months to 18 months (MET 2+/3+ population; HR 0.49). Enrollment stopped early due to negative final results from a phase II trial assessing mFOLFOX6 + Onartuzumab [136]. A total of 562 patients were enrolled, among them 39% were patients with MET 2+/3+ expression. In the ITT population, the overall survival was similar between the onartuzumab arm and placebo arm (11.0 months vs 11.3 months, HR 0.82, P = 0.244). In the MET2+/3+ population, the overall survival was also similar between the two arms (11.0 months vs 9.7 months, HR 0.64, P = 0.062). The progression-free survival and overall response rate were not improved by the addition of onartuzumab in all ITT population and MET2+/3+ population.

AMG337 is the highly selective small molecule inhibitor of MET. In a phase I study of AMG337, eight out of 13 (62%) *MET*-amplified gastric or gastroesophageal junction and esophageal cancer patients showed overall response [137]. Based on these data, there has been a phase II study of AMG337 monotherapy in *MET*-amplified gastric cancer patients who have failed at least 1 prior chemotherapy (ClinicalTrials.gov. NCT02016534). This study was stopped early.

FGFR

In gastric cancer, 4.2% of Korean patients and 7.4% of UK patients harbor *FGFR2* amplification, and intratumoral heterogeneity is observed in 24% of *FGFR2*-amplified cases [138]. About 20% of patients show FGFR2 polysomy. *FGFR2* amplification and polysomy are associated with worse overall survival in the Korean (1.83 years vs 6.17 years, $P = 0.0073$) and UK (0.45 years vs 1.9 years, $P < 0.0001$) cohorts. Preclinical study of AZD4547, a potent and selective ATP-competitive receptor tyrosine kinase inhibitor of FGFR 1–3, in FGFR2-amplified gastric cancer cells showed dramatic antitumor effects [139]. In a randomized phase II study, patients with disease progression after 1 prior line of therapy were assigned to FGFR2 amplified or polysomy arms and randomized to oral AZD4547 or paclitaxel (ClinicalTrials.gov. NCT01457846) [140]. The primary endpoint was progression-free survival. Of 960 patients enrolled, 71 patients were randomized. FGFR2 amplification prevalence was 9%. The overall progression-free survival was 1.8 months in the AZD4547 arm versus 3.5 months in the paclitaxel arm. In patients with FGFR2 amplification, the progression-free survival of AZD4547 was 1.5 months and that of paclitaxel was 2.3 months. Only 21% of FGFR2-amplified tumors had elevated FGFR2 expression and image analysis showed four out of seven tumor samples, highly amplified by FISH, were amplified in <20% of the tumor section. It means that there is marked intra-tumor heterogeneity of FGFR2 amplification and low concordance with elevated FGFR2 expression.

AKT/mTOR

Phosphatidylinositol 3-kinase (PI3K)/Akt and mammalian target of rapamycin (mTOR) are activated in 30% and 60% of gastric cancers, respectively [141, 142].

Everolimus is an oral mTOR inhibitor. The GRANITE-1 study (First Gastric Antitumor Trial with Everolimus) is an international, double-blind, phase III study that compared efficacy and safety of everolimus with that of best supportive care in previously treated advanced gastric cancer [143]. There was no patient selection based on biomarkers. A total of 656 patients whose disease progressed after one or two lines of systemic chemotherapy were enrolled and randomized to everolimus and placebo in a 2:1 ratio. The overall survival, the primary endpoint, was similar between the two arms (5.4 months in everolimus vs 4.3 months in placebo, HR 0.90, $P = 0.124$). Common grade 3/4 adverse events included anemia, decreased appetite, and fatigue.

MK2206 is the allosteric inhibitor of AKT. In a phase II study of MK2206 as second-line therapy, 70 patients were enrolled with no selection [144]. The response rate was 1%, the progression-free survival was 1.8 months, and the overall survival was 5.1 months. All grade adverse events were anemia (17%), anorexia (30%), diarrhea (26%), fatigue (50%), hyperglycemia (30%), nausea (40%), vomiting (22%), dry skin (19%), and maculopapular rash (30%). This study suggests that in an unselected population, the efficacy of AKT inhibitor monotherapy is not sufficient.

Ipatasertib (GDC-0068) is an oral, potent ATP-competitive small molecule inhibitor of all 3 isoforms of Akt that specifically targets cancer cells with activated Akt. The JAGUAR study is ongoing, which is a randomized phase II study of the ipatasertib versus placebo in combination with mFOLFOX6 in HER2-negative gastric or gastroesophageal junction adenocarcinoma (ClinicalTrials.gov. NCT01896531). The patient enrollment was completed and stratified by PTEN status.

PARP

Ataxia-telangiectasia mutated (ATM) gene is a component of DNA-damage response (DDR) and is activated by DNA double-strand breaks (DSBs), and signals the cell-cycle checkpoint to slow the passage of cells through the cycle to facilitate DNA repair. ATM loss was observed in 16% of human gastric cancer tissues [145]. Analysis of associations among MSI, ATM gene mutation, and ATM protein loss revealed highly co-existing ATM gene alterations and MSI [146]. Furthermore, genome-wide association studies (GWAS) in Asian and European populations have identified several loci that associate with gastric cancer risk [147]. Association of a new gastric cancer and loss-of-function mutations in ATM was found (gene test, $P = 8.0 \times 10[-12]$; odds ratio [OR] = 4.74).

Olaparib is a PARP inhibitor, inhibiting poly ADP ribose polymerase (PARP), an enzyme involved in DNA repair. Low ATM protein expression and depletion of p53 was reported to be correlated with olaparib sensitivity in gastric cancer cells [148].

A randomized, double-blind phase II study was conducted to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with gastric cancer [149]. A total of 124 patients were enrolled and the prevalence of ATM-low population was 14%. Patients were randomized to olaparib plus paclitaxel or placebo plus paclitaxel. Olaparib did not improve the progression-free survival compared with placebo not only in the overall population (3.91 months vs 3.55 months) but also in the ATM-low population (5.29 months vs 3.68 months, HR 0.74). However, interestingly enough, the olaparib arm showed significantly prolonged overall survival not only in the overall population (13.1 months vs 9.4 months, HR 0.56, $P = 0.005$) but also in the ATM-low population (median not reached vs 8.2 months, HR 0.35, $P = 0.002$). The combination treatment was generally well tolerated. Based on this finding, the phase III GOLD study was conducted to assess the efficacy and safety of olaparib in combination with paclitaxel in Asian patients with advanced gastric and gastroesophageal junction cancer who have progressed following first-line therapy (ClinicalTrials.gov. NCT01924533) [150]. This study had co-primary endpoints: one is overall survival in all patients, and the other was overall survival in ATM-negative population. With this, p value should be less than 0.025 to be

significant. However, this study failed to meet the primary endpoint. In all populations, overall survival was prolonged in the olaparib arm (median survival 6.9 vs 8.8 months; HR 0.79; 97% CI, 0.63 to 1.0; $P = 0.0262$); however, it did not reach statistical significance. In the ATM-negative population, median survival was 10.0 and 12.0 months, respectively, and there was no statistically significant difference (HR 0.73; 97% CI, 0.40 to 1.34; $P = 0.2458$).

Cancer Stem Cell

Subpopulations of cancer cells with extremely high tumorigenic potential, termed "cancer stem cells" or "stem-like cancer cells," have been isolated from cancer patients [151]. Such highly tumorigenic and drug-resistant stemness-high cancer stem cells are, therefore, likely to be involved in the resistance to chemotherapy or radiotherapy.

BBI608 is a small molecule to inhibit gene transcription driven by Stat3 and cancer stemness properties [152]. Through its action, BBI608 can inhibit stemness gene expression and block spherogenesis or kill stemness-high cancer cells.

The BRIGHTER study, the phase III trial of BBI608 plus paclitaxel versus placebo plus paclitaxel in second-line gastric and gastroesophageal junction cancer, is ongoing (ClinicalTrials.gov. NCT02178956). The target patient number is 700 and the primary endpoint is overall survival.

Immunotherapy

The idea of using immune cells to fight cancer, that is cancer immunotherapy, is not a new concept. However, only recently, the clinical successes of this harnessing immune cell strategy have been realized in solid tumors, especially using immune checkpoint inhibitors [153]. As opposed to mutated genes in tumors that permanently mark a tumor, the immune response is so dynamic and changes very rapidly. Therefore, the issue facing the field of cancer immunotherapy may not be the identification of a single biomarker to select a subset of patients for treatment. The tumor microenvironment is composed of multiple components such as tumor parenchymal cells, lymphocytes, fibroblast, mesenchymal cells, angiogenic factors, and so on. Cell-mediated immunity against cancer is based on effective interaction between macrophages and T cells [154]. The adaptive immune system plays a main role in fighting against cancer. In gastric cancer patients, peritumor infiltration of cytotoxic T cells and memory T is associated with better prognosis [155]. In the tumor microenvironment of gastric cancer, macrophages constitute one of the most abundant immune cells. Tumor-associated macrophage (TAM) infiltration leads to inhibition of T cells and is related to the poor prognosis [156, 157].

Immune checkpoint inhibitors that augment the anticancer immune response in gastric cancer include T lymphocyte antigen (CTLA)-4, anti-programmed death (PD)-1, and anti-PD ligand 1 (PD-L1).

CTLA-4 Inhibitor

CTLA-4 is a key negative regulator of T-cell activation. It is constitutively expressed on the cell surface of Treg and inducibly expressed on activated T lymphocytes and monocytes. Two fully humanized monoclonal antibodies against CTLA-4, ipilimumab, and tremelimumab have shown clinical activity in solid tumors. Tremelimumab is a fully human immunoglobulin G 2 (IgG2) monoclonal antibody that blocks the binding of B7–1 and B7–2 to CTLA-4 resulting in the inhibition of B7-CTLA-4 mediated downregulation of T-cell activation. It was developed as an IgG2 isotype to minimize complement activation and reduce the risk of cytokine storm; this has resulted in a long terminal phase half-life of 19.6 days, and a dosing schedule of once every 3 months. In a phase II study, tremelimumab was tested as a second-line treatment for 18 metastatic gastric or gastroesophageal adenocarcinoma patients [158]. Tremelimumab was given every 3 months until symptomatic disease progression. Most of the drug-related adverse events were mild; however, there was a single death due to colitis-induced bowel perforation. The overall survival was 4.8 months, which was a comparable result with those obtained by cytotoxic second-line chemotherapy, in general. The overall response rate was 5%. Four patients had stable disease with clinical benefit; one patient achieved a partial response after 8 cycles (25.4 months) and remains well on study at 32.7 months. Markers of regulatory phenotype, forkhead box protein 3 and CTLA-4, doubled transiently in CD4 + CD25 high lymphocytes in the first month after tremelimumab dosing before returning to baseline. In contrast, CTLA-4 increased in CD4 + CD25 low/negative lymphocytes throughout the cycle of treatment. De novo proliferative responses to tumor-associated antigens 5T4 (8 of 18 patients) and carcinoembryonic antigen (CEA) (5 of 13) were detected. Patients with a post-treatment CEA proliferative response had an overall survival of 17.1 months compared with 4.7 months for non-responders ($P = 0.004$). Baseline interleukin-2 release after T-cell activation was higher in patients with clinical benefit and toxicity.

Ipilimumab has been tested in a randomized, open-label, phase II trial (ClinicalTrials.gov. NCT01585987) [159]. This study was conducted to compare the efficacy of sequential ipilimumab versus BSC following first-line chemotherapy (fluoropyrimidine and platinum doublet) in patients with gastric or gastroesophageal junction cancer. Patients were randomized to ipilimumab (4 doses [10 mg/kg, IV Q3W], followed by Q12W) and treated until confirmed immune-related disease progression or unacceptable toxicity, or to best supportive care (continuing fluoropyrimidine chemotherapy or no active systemic therapy). The primary objective was to compare immune-related progression-free survival (irPFS). In this study, 79 of the patients in the BSC arm received fluoropyrimidine alone. The study was negative, and irPFS were 4.90 months in the BSC arm and 2.92 months in the ipilimumab arm.

PD-1/PD-L1 Inhibitor

PD-1 is another co-inhibitory receptor expressed on the surface of activated T cells, Treg cells, and monocytes. PD-1 induces a negative regulation of effector T cells by interacting with its ligands PD-L1 and PD-L2 on the tumor cells. The PD-L1 is expressed on many tumors and suppressive immune cells in the tumor microenvironment. Interaction of PD-1 and PD-L1 results in the inhibition of T-cell function.

In gastric cancer, high expression of PD-L1 on tumor cells was observed in 29.6% of patients and this PD-L1 expression was correlated with tumor infiltration of PD-1(+) cells [160]. Furthermore, PD-L1 expression was associated with worse overall survival. Another study also gave similar evidence that PD-1 expression was correlated with both PD-L1 and Foxp3 expression, and PD-1 expression was associated with a poor prognosis of gastric cancer patients [161].

Pembrolizumab is an anti-PD-1 antibody. The KEYNOTE-012 phase Ib study tested the efficacy and safety of pembrolizumab monotherapy in PD-L1 (+) gastric cancer patients [162]. In this study, PD-L1-positive expression was defined as staining in the stroma or in >1% of tumor cells by prototype IHC and 22C3 antibody. Using this method and definition, the PD-L1 (+) was observed in 40% (65 out of 162) of gastric cancer patients. Of these 65 patients, 39 patients were enrolled (19 from Asia-Pacific, 20 from non-Asian; median age, 63 years [range 33–78]). The number of prior therapies for advanced gastric cancer ranged from 0 to 5; 67% received ≥2 prior therapies. The overall response rate was 22% (95% CI 10–39) by central review and 33% (95% CI 19–50) by investigator review. Median time to response was 8 weeks (range 7–16), with a median response duration of 24 weeks (range 8+ to 33+). PD-L1 expression level was associated with the overall response rate (1-sided $P = 0.10$). The 6-month progression-free survival rate was 24%. The 6-month overall survival rate was 69%. Five patients (12.8%) experienced grade 3/4 treatment-related adverse events with an incidence greater than 3%, peripheral sensory neuropathy (grade 3, one patient), fatigue (grade 3, two patients), hypothyroidism (grade 3, one patient), pemphigoid (grade 3, one patient), and pneumonitis (grade 4, one patient.

A number of clinical trials using anti-PD-1 antibody or anti-PD-L1 antibody in gastric cancer are ongoing.

Conclusion

Gastric cancer is a huge burden of cancer-related mortality worldwide. However, with early diagnosis, good surgical techniques, proper adjuvant treatment, and development of new targeted agents and immune checkpoint inhibitors, the outcome of this dismal disease is being improved. Development of genetic information and biomarkers will lead to a more personalized approach in the near future.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN. Int J Cancer. 2012;2015136:E359–86.
2. Wang AY, Peura DA. The prevalence and incidence of Helicobacter pylori-associated peptic ulcer disease and upper gastrointestinal bleeding throughout the world. Gastrointest Endosc Clin N Am. 2011;21:613–35.
3. Parkin DM. The global health burden of infection-associated cancers in the year 2012. Int J Cancer. 2006;18:3030–4.
4. Yamaoka Y, Graham DY. Helicobacter pylori virulence and cancer pathogenesis. Future Oncol. 2014;10:1487–500.
5. Hanada K, Graham DY. Helicobacter pylori and the molecular pathogenesis of intestinal-type gastric carcinoma. Expert Rev Anticancer Ther. 2014;14:947–54.
6. Wei J, Nagy TA, Vilgelm A, Zaika E, Ogden SR, Romero-Gallo J, et al. Regulation of p53 tumor suppressor by Helicobacter pylori in gastric epithelial cells. Gastroenterology. 2010;139:1333–43.
7. Ushijima T, Asaka K. Aberrant DNA methylation in contrast with mutations. Cancer Sci. 2010;101:300–5.
8. Hayashi Y, Tsujii M, Wang J, Kondo J, Akasaka T, Jin Y, et al. CagA mediates epigenetic regulation to attenuate let-7 expression in Helicobacter pylori-related carcinogenesis. Gut. 2013;62:1536–46.
9. Augusto AC, Miguel F, Mendonça S, Pedrazzoli J Jr, Gurgueira SA. Oxidative stress expression status associated to Helicobacter pylori virulence in gastric diseases. Clin Biochem. 2007;40:615–22.
10. Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiologic evidence. Gastric Cancer. 2007;10:75–83.
11. Wang XQ, Terry PD, Yan H. Preview of salt consumption and stomach cancer risk: epidemiological and biological evidence. World J Gastroenterol. 2009;15:2204–13.
12. Guggenheim DE, Shah MA. Gastric cancer epidemiology and risk factors. J Surg Oncol. 2013;107:230–6.
13. Crane SJ, Locke GR 3rd, Harmsen WS, Diehl NN, Zinsmeister AR, Melton LJ 3rd, et al. Subsite-specific risk factors for esophageal and gastric adenocarcinoma. Am J Gastroenterol. 2007;102:1596–602.
14. Yaghoobi M, Bijarchi R, Narod SA. Family history and the risk of gastric cancer. Br J Cancer. 2010;102:237–42.
15. Marcos-Pinto R, Carneiro F, Dinis-Ribeiro M, Wen X, Lopes C, Figueiredo C, et al. First-degree relatives of patients with early-onset gastric carcinoma show even at young ages a high prevalence of advanced OLGA/OLGIM stages and dysplasia. Aliment Pharmacol Ther. 2012;35:1451–9.
16. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al., European Helicobacter Study Group. Management of Helicobacter pylori infection—the Maastricht IV/Florence Consensus Report. Gut. 2012;61:646–64.
17. Han MA, Oh MG, Choi IJ, Park SR, Ryu KW, Nam BH, et al. Association of family history with cancer recurrence and survival in patients with gastric cancer. J Clin Oncol. 2012;30:701–8.
18. Carvalho B, Buffart TE, Reis RM, Mons T, Moutinho C, Silva P, et al. Mixed gastric carcinomas show similar chromosomal aberrations in both their diffuse and glandular components. Cell Oncol. 2006;28(5–6):283–94.
19. Machado JC, Soares P, Carneiro F, Rocha A, Beck S, Blin N, et al. E-cadherin gene mutations provide a genetic basis for the phenotypic divergence of mixed gastric carcinomas. Lab Investig. 1999;79(4):459–65.
20. Tajima Y, Shimoda T, Nakanishi Y, Yokoyama N, Tanaka T, Shimizu K, et al. Gastric and intestinal phenotypic marker expression in gastric carcinomas and its prognostic significance: immunohistochemical analysis of 136 lesions. Oncology. 2001;61(3):212–20.

21. Zeng YJ, Zhang CD, Dai DQ. Impact of lymph node micrometastasis on gastric carcinoma prognosis: a meta-analysis. World J Gastroenterol. 2015;21(5):1628–35.
22. Lee HS, Kim MA, Yang HK, Lee BL, Kim WH. Prognostic implication of isolated tumor cells and micrometastases in regional lymph nodes of gastric cancer. World J Gastroenterol. 2005;11(38):5920–5.
23. Kim S, Chung JW, Jeong TD, Park YS, Lee JH, Ahn JY, et al. Searching for E-cadherin gene mutations in early onset diffuse gastric cancer and hereditary diffuse gastric cancer in Korean patients. Familial Cancer. 2013;12(3):503–7.
24. Valente P, Garrido M, Gullo I, Baldaia H, Marques M, Baldaque-Silva F, et al. Epithelial dysplasia of the stomach with gastric immunophenotype shows features of biological aggressiveness. Gastric Cancer. 2015;18(4):720–8.
25. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–9.
26. Deng N, Goh LK, Wang H, Das K, Tao J, Tan IB, et al. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. Gut. 2012;61(5):673–84.
27. Han N, Kim MA, Lee HS, Kim WH. Evaluation of fibroblast growth factor receptor 2 expression, heterogeneity and clinical significance in gastric cancer. Pathobiology. 2015;82(6):269–79.
28. Wang K, Yuen ST, Xu J, Lee SP, Yan HH, Shi ST, et al. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. Nat Genet. 2014;46(6):573–82.
29. Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015;21(5):449–56.
30. Lee MH, Choi D, Park MJ, Lee MW. Gastric cancer: imaging and staging with MDCT based on the 7th AJCC guidelines. Abdom Imaging. 2012;37:531–40.
31. Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. Endoscopy. 2010;42:705–13.
32. Yun M. Imaging of gastric cancer metabolism using 18 F-FDG PET/CT. J Gastric Cancer. 2014;14:1–6.
33. Ahn HS, Kim SH, Kodera Y, Yang HK. Gastric cancer staging with radiologic imaging modalities and UICC staging system. Dig Surg. 2013;30:142–9.
34. Hamashima C, Okamoto M, Shabana M, Osaki Y, Kishimoto T. Sensitivity of endoscopic screening for gastric cancer by the incidence method. Int J Cancer. 2013;133:653–9.
35. Kawahara Y, Takenaka R, Okada H. Novel chromoendoscopic method using an acetic acid-indigocarmine mixture for diagnostic accuracy in delineating the margin of early gastric cancers. Dig Endosc. 2009;21:14–9.
36. Park HA, Nam SY, Lee SK, Kim SG, Shim KN, Park SM, et al. The Korean guideline for gastric cancer screening. J Korean Med Assoc. 2015;58:373–84.
37. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut. 2001;48:225–9.
38. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol. 2005;23:4490–8.
39. Yoon H, Kim SG, Choi J, Im JP, Kim JS, Kim WH, et al. Risk factors of residual or recurrent tumor in patients with a tumor-positive resection margin after endoscopic resection of early gastric cancer. Surg Endosc. 2013;27:1561–8.
40. Lim JH, Kim SG, Choi J, Im JP, Kim JS, Jung HC. Risk factors for synchronous or metachronous tumor development after endoscopic resection of gastric neoplasms. Gastric Cancer. 2015;18:817–23.
41. Choi J, Kim SG, Yoon H, Im JP, Kim JS, Kim WH, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. Clin Gastroenterol Hepatol. 2014;12:793–800.
42. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomized controlled trial. Lancet. 2008;372:392–7.
43. Choi J, Kim SG, Im JP, Kim JS, Jung HC. Long-term clinical outcomes of endoscopic resection for early gastric cancer. Surg Endosc. 2015;29:1223–30.
44. Association JGC. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14(2):113–23.
45. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma–2nd English edition. Gastric Cancer. 1998;1(1):10–24.
46. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet. 1996;347(9007):995–9.
47. Bonenkamp J, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, et al., Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. N Engl J Med.1999;340(12):908–14.
48. Degiuli M, Sasako M, Ponti A, Vendrame A, Tomatis M, Mazza C, et al., Italian Gastric Cancer Study Group. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg. 2014;101(2):23–31.
49. Markar SR, Karthikesalingam A, Jackson D, Hanna GB. Long-term survival after gastrectomy for cancer in randomized, controlled oncological trials: comparison between West and East. Ann Surg Oncol. 2013;20(7):2328–38.
50. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol. 2010;11(5):439–49.
51. Cuschieri A, Hanna GB. Meta-analysis of d1 versus d2 gastrectomy for gastric adenocarcinoma: let us move on to another era. Ann Surg. 2014;259(6):e90.
52. Schmidt B, Chang KK, Maduekwe UN, Look-Hong N, Rattner DW, Lauwers GY, et al. D2 lymphadenectomy with surgical ex vivo dissection into node stations for gastric adenocarcinoma can be performed safely in Western patients and ensures optimal staging. Ann Surg Oncol. 2013;20(9):2991–9.
53. Ahn H, Lee H, Hahn S, Kim WH, Lee KU, Sano T, et al. Evaluation of the Seventh American Joint Committee on Cancer/International Union Against Cancer Classification of gastric adenocarcinoma in comparison with the sixth classification. Cancer. 2010;116(24):5592–8.
54. Lee SW, Nomura E, Bouras G, Tokuhara T, Tsunemi S, Tanigawa N. Long-term oncologic outcomes from laparoscopic gastrectomy for gastric cancer: a single-center experience of 601 consecutive resections. J Am Coll Surg. 2010;211(1):33–40.
55. Qiu MZ, Wang ZQ, Zhang DS, Liu Q, Luo HY, Zhou ZW, et al. Comparison of 6th and 7th AJCC TNM staging classification for carcinoma of the stomach in China. Ann Surg Oncol. 2011;18(7):1869–76.
56. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. Surg Laparosc Endosc Percutan Tech. 1994;4(2):146–8.
57. Kim W, Kim HH, Han SU, Kim MC, Hyung WJ, Ryu SW, et al., Korean Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric

cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS-01). Ann Surg. 2016;263(1):28–35.
58. The KLASS-01 trial revealed similar overall and cancer-specific survival rates between patients receiving laparoscopic and open distal gastrectomy. JAMA Oncol. 2019; https://doi.org/10.1001/jamaoncol.2018.6727. [Epub ahead of print].
59. Kim HH, Han SU, Kim MC, Hyung WJ, Kim W, Lee HJ, et al. Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case-control and case-matched Korean multicenter study. J Clin Oncol. 2014;32(7):627–33.
60. Han TS, Kong SH, Lee HJ, Ahn HS, Hur K, Yu J, et al. Dissemination of free cancer cells from the gastric lumen and from perigastric lymphovascular pedicles during radical gastric cancer surgery. Ann Surg Oncol. 2011;18(10):2818–25.
61. Kuramoto M, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. Ann Surg. 2009;250(2):242–6.
62. Maki T, Shiratori T, Hatafuku T, Sugawara K. Pylorus-preserving gastrectomy as an improved operation for gastric ulcer. Surgery. 1967;61(6):838–45.
63. Park DJ, Lee HJ, Jung HC, Kim WH, Lee KU, Yang HK. Clinical outcome of pylorus-preserving gastrectomy in gastric cancer in comparison with conventional distal gastrectomy with Billroth I anastomosis. World J Surg. 2008;32(6):1029–36.
64. Nunobe S, Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Symptom evaluation of long-term postoperative outcomes after pylorus-preserving gastrectomy for early gastric cancer. Gastric Cancer. 2007;10(3):167–72.
65. Suh YS, Han DS, Kong SH, Kwon S, Shin CI, Kim WH, et al. Laparoscopy-assisted pylorus-preserving gastrectomy is better than laparoscopy-assisted distal gastrectomy for middle-third early gastric cancer. Ann Surg. 2014;259(3):485–93.
66. Jiang X, Hiki N, Nunobe S, Fukunaga T, Kumagai K, Nohara K, et al. Postoperative outcomes and complications after laparoscopy-assisted pylorus-preserving gastrectomy for early gastric cancer. Ann Surg. 2011;253(5):928–33.
67. Kong SH, Kim JW, Lee HJ, Kim WH, Lee KU, Yang HK. The safety of the dissection of lymph node stations 5 and 6 in pylorus-preserving gastrectomy. Ann Surg Oncol. 2009;16(12):3252–8.
68. Yoo MW, Park DJ, Ahn HS, Jeong SH, Lee HJ, Kim WH, et al. Evaluation of the adequacy of lymph node dissection in pylorus-preserving gastrectomy for early gastric cancer using the maruyama index. World J Surg. 2010;34(2):291–5.
69. Sigstad H. A clinical diagnostic index in the diagnosis of the dumping syndrome. Acta Med Scand. 1970;188(1–6):479–86.
70. Song J, Oh SJ, Kang WH, Hyung WJ, Choi SH, Noh SH. Robot-assisted gastrectomy with lymph node dissection for gastric cancer: lessons learned from an initial 100 consecutive procedures. Ann Surg. 2009;249(6):927–32.
71. Yoon HM, Kim YW, Lee JH, Ryu KW, Eom BW, Park JY, et al. Robot-assisted total gastrectomy is comparable with laparoscopically assisted total gastrectomy for early gastric cancer. Surg Endosc. 2012;26(5):1377–81.
72. Wall J, Marescaux J. Robotic gastrectomy is safe and feasible, but real benefits remain elusive: comment on "robotic gastrectomy as an oncologically sound alternative to laparoscopic resections for the treatment of early-stage gastric cancers". Arch Surg. 2011;146(9):1092.
73. Park JY, Jo MJ, Nam BH, Kim Y, Eom BW, Yoon HM, et al. Surgical stress after robot-assisted distal gastrectomy and its economic implications. Br J Surg. 2012;99(11):1554–61.
74. Kim HI, Han SU, Yang HK, Kim YW, Lee HJ, Ryu KW, et al. Multicenter prospective comparative study of robotic versus laparoscopic gastrectomy for gastric adenocarcinoma. Ann Surg. 2016;263(1):103–9.
75. Oh DY, Bang YJ. Adjuvant and neoadjuvant therapy for gastric cancer. Curr Treat Options in Oncol. 2013;14(3):311–20.
76. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725–30.
77. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol. 2012;30(19):2327–33.
78. Fuchs CS, Tepper JE, Niedzwiecki D, Hollis D, Mamon HJ, Swanson R, et al., Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: intergroup trial CALGB 80101. J Clin Oncol. 2011;29(15 Suppl):S4003.
79. Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol. 2012;30:268–73.
80. Park SH, Sohn TS, Lee J, Lim DH, Hong ME, Kim KM, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol. 2015;33(28):3130–6.
81. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al., MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
82. Cunningham D, Chua YJ. East meets west in the treatment of gastric cancer. N Engl J Med. 2007;357:1863–5.
83. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29:1715–21.
84. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al., ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810–20.
85. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29:4387–93.
86. Bang YJ, Kim YW, Yang HK Chung HC, Park YK, Lee KH, et al., CLASSIC Trial Investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379(9813):315–21.
87. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, et al., CLASSIC Trial Investigators. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(12):1389–96.
88. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24(18):2903–9.
89. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al., V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24(31):4991–7.

90. Dank M, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol. 2008;19(8):1450–7.
91. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9(3):215–21.
92. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28(9):1547–53.
93. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358(1):36–46.
94. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009;20(4):666–73.
95. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al., Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10(11):1063–9.
96. Guimbaud R, Louvet C, Ries P, Ychou M, Maillard E, André T, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. J Clin Oncol. 2014;32(31):3520–6.
97. Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol. 2012;30(13):1513–8.
98. Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al., COUGAR-02 Investigators. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15(1):78–86.
99. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.
100. Van Cutsem E, Bang YJ, Feng-Yi F, Xu JM, Lee KW, Jiao SC, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer. 2015;18(3):476–84.
101. Bang YJ. Advances in the management of HER2-positive advanced gastric and gastroesophageal junction cancer. J Clin Gastroenterol. 2012;46(8):637–48.
102. Cappellesso R, Fassan M, Hanspeter E, Bornschein J, d'Amore ES, Cuorvo LV, et al. HER2 status in gastroesophageal cancer: a tissue microarray study of 1040 cases. Hum Pathol. 2015;46(5):665–72.
103. Hofmann M, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52:797–805.
104. Kurokawa Y, Sugimoto N, Miwa H, Tsuda M, Nishina S, Okuda H, et al. Phase II study of trastuzumab in combination with S-1 plus cisplatin in HER2-positive gastric cancer (HERBIS-1). Br J Cancer. 2014;110:1163–8.
105. Gravalos C, Gomez-Martin C, Rivera F, Ales I, Queralt B, Marquez A, et al. Phase II study of trastuzumab and cisplatin as first-line therapy in patients with HER2-positive advanced gastric or gastroesophageal junction cancer. Clin Transl Oncol. 2011;13:179–84.
106. Gomez-Martin C, Plaza JC, Pazo-Cid R, Salud A, Pons F, Fonseca P, et al. Level of HER2 gene amplification predicts response and overall survival in HER2-positive advanced gastric cancer treated with trastuzumab. J Clin Oncol. 2013;31:4445–52.
107. Ock CY, Lee KW, Kim JW, Kim JS, Kim TY, Lee KH, et al. Optimal patient selection for trastuzumab treatment in HER2-positive advanced gastric cancer. Clin Cancer Res. 2015;21(11):2520–9.
108. Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. J Clin Oncol. 2014;32(19):2039–49.
109. Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2–positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC— a randomized phase III trial. J Clin Oncol. 2016;34(5):443–51.
110. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. Cancer Res. 2004;64:2343–6.
111. Scheuer W, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. Cancer Res. 2009;69(24):9330–6.
112. Yamashita-Kashima Y, Iijima S, Yorozu K, Furugaki K, Kurasawa M, Ohta M, et al. Pertuzumab in combination with trastuzumab shows significantly enhanced antitumor activity in HER2-positive human gastric cancer xenograft models. Clin Cancer Res. 2011;17:5060–70.
113. Kang YK, Rha SY, Tassone P, Barriuso J, Yu R, Szado T, et al. A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer. Br J Cancer. 2014;111(4):660–6.
114. Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastrooesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19(10):1372–84.
115. Thuss-Patience PC, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017;18:640–53.
116. Liu L, Ma XL, Xiao ZL, Li M, Cheng SH, Wei YQ. Prognostic value of vascular endothelial growth factor expression in resected gastric cancer. Asian Pac J Cancer Prev. 2012;13(7):3089–97. Review.
117. Ji YN, Wang Q, Li Y, Wang Z. Prognostic value of vascular endothelial growth factor a expression in gastric cancer: a meta-analysis. Tumour Biol. 2014;35(3):2787–93.
118. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol. 2011;29(30):3968–76.
119. Shen L, Li J, Xu J, Pan H, Dai G, Qin S, et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). Gastric Cancer. 2015;18(1):168–76.

120. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al., REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9.
121. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al., RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224–35.
122. Fuchs CS, Shitara K, Di Bartolomeo M, Lonardi S, Al-Batran SE, Van Cutsem E, Ilson DH, Alsina M, Chau I, Lacy J, Ducreux M, Mendez GA, Alavez AM, Takahari D, Mansoor W, Enzinger PC, Gorbounova V, Wainberg ZA, Hegewisch-Becker S, Ferry D, Lin J, Carlesi R, Das M, Shah MA, RAINFALL Study Group. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(3):420–35.
123. Li J, Qin S, Xu J, Guo W, Xiong J, Bai Y, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. J Clin Oncol. 2013;31(26):3219–25.
124. Qin S. Phase III study of apatinib in advanced gastric cancer: a randomized, double-blind, placebo-controlled trial. 2014 ASCO Annual Meeting. J Clin Oncol. 2014;32:5s.. (suppl; abstr 4003).
125. Pavlakis N, Sjoquist KM, Martin AJ, Tsobanis E, Yip S, Kang YK, et al. Regorafenib for the treatment of advanced gastric cancer (INTEGRATE): a multinational placebo-controlled phase II trial. J Clin Oncol. 2016;34(23):2728–35.
126. Kim MA, Lee HS, Lee HE, Jeon YK, Yang HK, Kim WH. EGFR in gastric carcinomas: prognostic significance of protein overexpression and high gene copy number. Histopathology. 2008;52:738–46.
127. Lordick F, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, et al., Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14(6):490–9.
128. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14(6):481–9.
129. Okines AF, Ashley SE, Cunningham D, Oates J, Turner A, Webb J, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for advanced esophagogastric cancer: dose-finding study for the prospective multicenter, randomized, phase II/III REAL-3 trial. J Clin Oncol. 2010;28:3945–50.
130. Satoh T, Lee KH, Rha SY, Sasaki Y, Park SH, Komatsu Y, et al. Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. Gastric Cancer. 2015;18(4):824–32.
131. Lee HE, Kim MA, Lee HS, Jung EJ, Yang HK, Lee BL, et al. MET in gastric carcinomas: comparison between protein expression and gene copy number and impact on clinical outcome. Br J Cancer. 2012;107(2):325–33.
132. Tanaka K, Miki C, Wakuda R, Kobayashi M, Tonouchi H, Kusunoki M. Circulating level of hepatocyte growth factor as a useful tumor marker in patients with early-stage gastric carcinoma. Cand J Gastroenterol. 2004;39:754–60.
133. Iveson T, Donehower RC, Davidenko I, Tjulandin S, Deptala A, Harrison M, et al. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. Lancet Oncol. 2014;15(9):1007–18.
134. Cunningham D, Tebbutt NC, Davidenko I, Murad AM, Al-Batran S-E, Ilson DH, et al. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. 2015 ASCO annual meeting. J Clin Oncol. 2015;33 (suppl; abstr 4000).
135. Shah MA, Bang YJ, Lordick F, Cunningham D. Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: the METGastric randomized clinical trial. JAMA Oncol. 2017;3(5):620–7.
136. Shah MA, Cho JY, Tan IB, Tebbutt NC, Yen CJ, Kang A, et al. A randomized phase II study of FOLFOX with or without the MET inhibitor onartuzumab in advanced adenocarcinoma of the stomach and gastroesophageal junction. Oncologist. 2016;21(9):1085–90.
137. Kwak EL, LoRusso P, Hamid O, Janku F, Kittaneh, M, Catenacci DVT, et al. Clinical activity of AMG 337, an oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer. 2015 ASCO Gastrointestinal Cancers Symposium. J Clin Oncol. 2015;33 (suppl 3; abstr 1).
138. Su X, Zhan P, Gavine PR, Morgan S, Womack C, Ni X, et al. FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study. Br J Cancer. 2014;110(4):967–75.
139. Xie L, Su X, Zhang L, Yin X, Tang L, Zhang X, et al. FGFR2 gene amplification in gastric cancer predicts sensitivity to the selective FGFR inhibitor AZD4547. Clin Cancer Res. 2013;19(9):2572–83.
140. Bang YJ, Van Cutsem E, Mansoor W, Petty RD, Chao Y, Cunningham D, et al. A randomized, open-label phase II study of AZD4547 (AZD) versus Paclitaxel (P) in previously treated patients with advanced gastric cancer (AGC) with Fibroblast Growth Factor Receptor 2 (FGFR2) polysomy or gene amplification (amp): SHINE study. 2015 ASCO Annual Meeting. J Clin Oncol. 2015;33 (suppl; abstr 4014).
141. Lang SA, Gaumann A, Koehl GE, Seidel U, Bataille F, Klein D, et al. Mammalian target of rapamycin is activated in human gastric cancer and serves as a target for therapy in an experimental model. Int J Cancer. 2007;120(8):1803–10.
142. Oki E, Baba H, Tokunaga E, Nakamura T, Ueda N, Futatsugi M, et al. Akt phosphorylation associates with LOH of PTEN and leads to chemoresistance for gastric cancer. Int J Cancer. 2005;117:376–80.
143. Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol. 2013;31(31):3935–43.
144. Ramanathan RK, McDonough SL, Kennecke HF, Iqbal S, Baranda JC, Seery TE, et al. Phase 2 study of MK-2206, an allosteric inhibitor of AKT, as second-line therapy for advanced gastric and gastroesophageal junction cancer: a SWOG cooperative group trial (S1005). Cancer. 2015;121(13):2193–7.
145. Kim HS, Kim MA, Hodgson D, Harbron C, Wellings R, O'Connor MJ, et al. Concordance of ATM (ataxia telangiectasia mutated) immunohistochemistry between biopsy or metastatic tumor samples and primary tumors in gastric cancer patients. Pathobiology. 2013;80:127–37.
146. Kim HS, Choi SI, Min HL, Kim MA, Kim WH. Mutation at intronic repeats of the ataxia-telangiectasia mutated (ATM) gene

and ATM protein loss in primary gastric cancer with microsatellite instability. PLoS One. 2013;8(12):e82769.
147. Helgason H, Rafnar T, Olafsdottir HS, Jonasson JG, Sigurdsson A, Stacey SN, et al. Loss-of-function variants in ATM confer risk of gastric cancer. Nat Genet. 2015;47(8):906–10.
148. Kubota E, Williamson CT, Ye R, Elegbede A, Peterson L, Lees-Miller SP, et al. Low ATM protein expression and depletion of p53 correlates with olaparib sensitivity in gastric cancer cell lines. Cell Cycle. 2014;13(13):2129–37.
149. Bang YJ, Im SA, Lee KW, Cho JY, Song EK, Lee KH, et al. Randomized, double-blind phase II trial with prospective classification by ATM protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer. J Clin Oncol. 2015;33(33):3858–65.
150. Bang YJ, Boku N, Chin K, Lee K-W, Park SH, Qin S, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy: phase III GOLD study. Ann Oncol. 2016;27(suppl 6):LBA25.
151. Visvader JE, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. Nat Rev Cancer. 2008;8(10):755–68.
152. Li Y, Rogoff HA, Keates S, Gao Y, Murikipudi S, Mikule K, et al. Suppression of cancer relapse and metastasis by inhibiting cancer stemness. Proc Natl Acad Sci U S A. 2015;112(6):1839–44.
153. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56–61.
154. Blankenstein T, Coulie PG, Gilboa E, Jaffee EM. The determinants of tumour immunogenicity. Nat Rev Cancer. 2012;12(4):307–13.
155. Amedei A, Della Bella C, Silvestri E, Prisco D, D'Elios MM. T cells in gastric cancer: friends or foes. Clin Dev Immunol. 2012;2012:690571.
156. Ishigami S, Natsugoe S, Tokuda K, Nakajo A, Okumura H, Matsumoto M, et al. Tumor-associated macrophage (TAM) infiltration in gastric cancer. Anticancer Res. 2003;23(5):4079–83.
157. Mitchem JB, Brennan DJ, Knolhoff BL, Belt BA, Zhu Y, Sanford DE, et al. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res. 2013;73(3):1128–41.
158. Ralph C, Elkord E, Burt DJ, O'Dwyer JF, Austin EB, Stern PL, et al. Modulation of lymphocyte regulation for cancer therapy: a phase II trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. Clin Cancer Res. 2010;16(5):1662–72.
159. Moehler MH, Cho JY, Kim EH, Kim JW, Di Bartolomeo M, Ajani JA, et al. A randomized, open-label, two-arm phase 2 trial comparing the efficacy of sequential ipilimumab versus best supportive care following first-line chemotherapy in patients with unresectable, locally advanced/metastatic gastric or gastroesophageal junction cancer. 2016 ASCO Annual Meeting. J Clin Oncol. 2016;34 (suppl; abstr 4011).
160. Tamura T, Ohira M, Tanaka H, Muguruma K, Toyokawa T, Kubo N, et al. Programmed Death-1 Ligand-1 (PDL1) expression is associated with the prognosis of patients with stage II/III gastric cancer. Anticancer Res. 2015;35(10):5369–76.
161. Eto S, Yoshikawa K, Nishi M, Higashijima J, Tokunaga T, Nakao T, et al. Programmed cell death protein 1 expression is an independent prognostic factor in gastric cancer after curative resection. Gastric Cancer. 2016;19(2):466–71.
162. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol. 2016;17(6):717–26.

Small Bowel and Appendix Cancers

6

Astrid Belalcazar-Portacio, Walid L. Shaib, and Bassel F. El-Rayes

Small Bowel Malignancies

The annual incidence of small bowel malignancies in the United States is 0.6% [1]. Small bowel malignancies are a heterogeneous group of tumors that include adenocarcinoma, neuroendocrine tumor (NET), lymphoma, and sarcoma. The incidence of neuroendocrine tumors (NETs) has increased over the last 30 years. NETs account for 44% of all small bowel tumors, which makes it the most common histology. Adenocarcinomas, lymphomas, and sarcoma represent 33%, 15%, and 8% of new cases on small bowel tumors, respectively.

Adenocarcinoma (Nonampullary)

Epidemiology

Small bowel (SB) adenocarcinoma patients have a median age at diagnosis of 65 years. Males have a higher incidence than females. Some studies have shown that in the Untied States, no difference in incidence according to ethnicity has been observed [2, 3]. Most small bowel adenocarcinomas arise in the duodenum (65%), followed by jejunum, (16%), and ileum (14%) [4, 5].

Clinical Presentation and Diagnosis

Symptoms of small bowel carcinoma include abdominal pain, nausea, vomiting, and anemia. Less than 10% of the patients may present with gastrointestinal (GI) bleeding, jaundice, or weight loss. Some patient's may present initially with small bowel obstruction or perforation [5].

Small bowel adenocarcinomas are commonly diagnosed at an advanced stage due to the lack of specific symptoms. Enhanced computed tomography (CT) or magnetic resonance imaging (MRI) is helpful for characterization of the tumor and evaluation of distant metastasis [6–8]. Positron emission tomography (PET)/CT also detects primary lesion and metastasis. No formal comparison of PET, CT, and MRI has been performed in SB adenocarcinoma [9]. The role of PET is to evaluate lesions that are indeterminate by cross-sectional imaging.

Prognosis and Staging

Clinical stage is the most important prognostic factor. The eighth edition of the tumor-node-metastasis (TNM) staging by the American Joint Committee on Cancer (AJCC) is used for staging of small bowel adenocarcinoma (Table 6.1) [10]. The 5-year survival by stage is 65% for stage I disease, 48% for stage II, 35% for stage III, and 4% for stage IV. Poor prognostic factors include advanced age, African American ethnicity, duodenal location, T4 lesions, poorly differentiated histology, positive margins, and lymph node involvement [11]. By location, 5-year overall survival (OS) is 28% for duodenal adenocarcinomas and 38% for jejunal and ileal adenocarcinomas [2, 3].

A. Belalcazar-Portacio
Department of Hematology and Medical Oncology, Northern Light Eastern Maine Medical Center, Lafayette Family Cancer Center, Brewer, ME, USA

W. L. Shaib
Department of Hematology and Medical Oncology, Emory University, Winship Cancer Institute, Atlanta, GA, USA

B. F. El-Rayes (✉)
Clinical Research, Department of Hematology and Medical Oncology, Emory University School of Medicine/Winship Cancer Institute of Emory University, Atlanta, GA, USA
e-mail: bassel.el-rayes@emoryhealthcare.org

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_6

Table 6.1 Small bowel adenocarcinoma TNM staging

Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia/carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T1a	Tumor invades lamina propria
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration[a]
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (e.g., other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)

[a]*Note*: For T3 tumors, the nonperitonealized perimuscular tissue is for the jejunum and ileum, part of the mesentery, and for the duodenum in areas where serosa is lacking, part of the interface with the pancreas

Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three or more regional lymph nodes

Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis present

AJCC prognostic stage groups			
Adenocarcinoma			
When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1–2	N0	M0	I
T3	N0	M0	IIA
T4	N0	M0	IIB
Any T	N1	M0	IIIA
Any T	N2	M0	IIIB
Any T	Any N	M1	IV

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

Treatment

Localized Early Stage Disease

The standard of care for early stage disease is surgical resection. Although there is no consensus regarding the best surgical method, it is agreed upon that the goal of surgery should be achieving complete resection with negative margins. For early stage (Tis, T1) tumors involving the first and/or second part of the duodenum, there are conflicting data regarding the role of pancreaticoduodenectomy vs. wide segmental resection [12, 13]. Tumors beyond the second portion of the duodenum are usually treated by segmental bowel resection. Resection must include removal of regional draining lymph nodes.

The role of adjuvant chemotherapy or radiation has not been evaluated in randomized prospective trials [5, 14, 15]. Recommendations for adjuvant therapy are based on the experience from management of colorectal cancer. For tumors beyond the second portion of the duodenum, presence of high-risk features such as T4, involvement of lymph nodes, or obstruction should prompt a discussion about adjuvant therapy. If considered, adjuvant therapy would be based on data from colorectal cancer and include 6 months of 5-fluorouracil (5-FU)-based regimen.

Advanced and Metastatic Disease

The treatment of advanced stage disease is based on retrospective trials. Chemotherapy seems to improve OS (10.7–18.6 months) compared to best supportive care (BSC) (2–13%). The response rate (RR) to chemotherapy varies a lot, from as low as 5% to 48% in some studies [4, 5, 16–18]. The combination of 5-FU with a platinum agent may improve progression-free survival (PFS) by 5 months, and showed a RR of 30%, but there is no evidence of improvement in OS [19]. Irinotecan has reported a RR of 20% [20]. Once again, treatment selection is mostly based on evidence in colorectal adenocarcinoma with 5-FU-based regimens.

The used of targeted therapies has not been extensively studied either. There are only a few case reports available, therefore no recommendations can be derived from these [21, 22].

Ampullary Adenocarcinoma

Ampullary adenocarcinoma refers to tumors arising in the ampullary complex. Ampullary tumors are classified as pancreatobiliary or intestinal subtype. The most common histology identified in ampullary neoplasms is intestinal (CDX positive, MUC1 negative) in 47% of cases, followed by pancreatobiliary (CDX negative, MUC1 positive) in 24% of cases [23]. As with colorectal cancer, K-ras mutations incidence is high ampullary adenocarcinoma (37%) [24]. The fact that these tumors are more frequent in patients with familial adenomatous polyposis (FAP) who also have a higher incidence of colorectal cancer, points to a similar etiology [25].

Epidemiology and Risk Factors

The most frequent location of small bowel adenocarcinomas is the ampulla of Vater, which is responsible for 20% of

tumor-related obstructions of the common bile duct [26, 27]. Median age at diagnosis is in the range of 60–70 years old for sporadic tumors [28, 29]. Patients with hereditary polyposis syndromes present at a younger age [25, 30]. The incidence of ampullary adenocarcinoma in patients with FAP and hereditary nonpolyposis colorectal cancer (HNPCC) is approximately 200 times higher compared to the general population [25, 30].

Clinical Presentation and Diagnosis

Ampullary tumors present early in the course of the disease due to bile duct obstruction. Jaundice is present at diagnosis in more than 65% of patients [31]. Other symptoms are abdominal pain or discomfort, nausea, vomiting, and weight loss [32]. Initial studies usually include abdominal ultrasound and CT scan. Endoscopic retrograde cholangiopancreatography (ERCP) can be used for tumor biopsy and decompression of the bile duct and as such has a central role in the diagnosis and management of ampullary adenocarcinoma.

Staging and Prognosis

The AJCC/International Union Against Cancer (UICC) TNM system has a specific staging system for ampullary carcinoma and is the most commonly used (see Table 6.2).

Surveillance, Epidemiology and End Results (SEER) database analysis of patients with ampullary carcinoma reported a 5-year OS for patients with stage I is 57–60%, for stage II, it is 22–30%, for stage III, it is 27%, and for stage IV, it is 0% [29]. Another study showed that being alive at 5 years post pancreaticoduodenectomy correlated with being alive at 10 years [33]. The 5-year OS based on surgical pathology staging is 84% in stage I patients, 70% in stage II patients, 27% in stage III patients, and 0% in stage IV patients [34].

Positive surgical margins are associated with poor prognosis, patients with R1 resection had 15% OS at 5 years compared to 60% in patients with R0 resection [35]. Nodal involvement also predicts worse survival; 5-year OS is 48% for patients without nodal involvement compared to 21% for patients with regional lymph node metastasis [29]. A better outcome has been described in patients with intestinal subtype compared to pancreatobiliary subtype, with a median survival of 116 months vs. 16 months, respectively [36]. Another study found a median OS (mOS) of 63.1 months vs. 43.2 months for patients with intestinal vs. pancreatobiliary type, respectively [37]. In addition to stage, poor prognostic factors reported by some studies include obstructive jaundice, requirement of intraoperative blood transfusion, and elevated cancer antigen 19-9 (CA 19-9) or carcinoembriogenic antigen (CEA) [38–40].

Table 6.2 Ampullary carcinoma TNM staging

Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T1	Tumor invades the mucosa or submucosa only and is ≤1 cm (duodenal tumors); Tumor ≤ 1 cm and confined within the sphincter of Oddi (ampullary tumors)
T2	Tumor invades the muscularis propria or is >1 cm (duodenal); Tumor invades through sphincter into duodenal submucosa or muscularis propria, or is >1 cm (ampullary)
T3	Tumor invades the pancreas or peripancreatic adipose tissue
T4	Tumor invades the visceral peritoneum (serosa) or other organs

Note: Multiple tumors should be designated as such (and the largest tumor should be used to assign the T category):
If the number of tumors is known, use T(#); e.g., pT3(4)N0M0
If the number of tumors is unavailable or too numerous, use the suffix m—T(m)—e.g., pT3(m)N0M0

Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement

Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

AJCC prognostic stage groups

When T is…	And N is…	And M is…	Then the stage group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	II
T4	N0	M0	III
Any T	N1	M0	III
Any T	Any N	M1	IV

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

Treatment

Localized Early Stage Disease

Surgery

Whipple resection (pancreaticoduodenectomy) is considered the standard of care for ampullary malignancies. The con-

ventional approach includes antrectomy whereas the modified approach preserves the pylorus. No difference in long-term survival has been demonstrated between these techniques. Historically, Whipple resection has been considered a surgery with high perioperative morbidity and mortality; however, outcomes have improved with a 30-day mortality less than 5%. Morbidity rates are 20–40% frequently due to anastomosis leak, delayed gastric emptying, or intraabdominal infections [41, 42].

Adjuvant Therapy

A report of 125 patients with ampullary carcinoma found that among patients with regional node involvement, the group that received adjuvant radiation with 5-FU (n = 29) had better survival than patients who underwent surgery only [43]. However, other studies did not find a significant difference in outcomes when adding adjuvant chemoradiation [43–45]. The European Study Group for Pancreatic Cancer (ESPAC)-3 trial studied 428 patients with resected periampullary malignancies including 297 ampullary, 96 bile duct, and 35 cases arising from other locations. Patients were randomized to either 5-FU, gemcitabine, or observation. In a subgroup analysis of patients with ampullary carcinoma, median survival was 71 months for patients treated with gemcitabine, 57.8 months in the 5-FU group, and 41 months among patients in the control group [46].

There is no expert consensus regarding the use of adjuvant therapy and this is reflected in the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines. Adjuvant chemoradiation is the most frequent adjuvant therapy used in the United States based on evidence from the Radiation Therapy Oncology Group (RTOG) 9704 trial, showing high risk of recurrence in patients with resected pancreatic adenocarcinoma [47, 48]. In Europe, chemotherapy alone is used for adjuvant treatment based on results from the ESPAC-3 and German Charité Onkologie (CONKO) trials [46, 48].

Locally Advanced or Metastatic Disease

Most of the data available for treatment of advanced ampullary carcinoma come from studies that included other types of GI malignancies. There are no consensus or guidelines in place for treatment of advanced stage ampullary carcinoma. The advanced biliary cancer (ABC) trial, a randomized phase 2 study of gemcitabine with or without cisplatin in patients with biliary cancer, included ampullary adenocarcinomas. There was better PFS (8 months vs. 5 months) and OS (11.7 months vs. 8.1 months) in the combination group compared to gemcitabine alone. However, the percentage of patients with ampullary cancer was small. A database analysis that included patients with either duodenal or ampullary adenocarcinomas showed a tendency in clinical practice to treat intestinal-type ampullary adenocarcinoma with fluorouracil-based regimens and pancreatobiliary type with gemcitabine-based regimens [37]. Intestinal subtypes seem to do better, but it remains unclear how much can be attributed to the chemotherapy regimen.

Appendiceal Tumors

Histologically, appendiceal malignancies are subdivided in epithelial, nonepithelial, or mixed-origin neoplasms. The first group includes adenocarcinoma (mucinous, colonic, and signet cell subtypes). The nonepithelial neoplasms include neuroendocrine tumors (NETs) of the appendix, and goblet cell carcinoids represent the mixed histology.

Epidemiology

Cancer of the appendix is an uncommon disease, found in approximately 1% of all appendectomies [49]. Similar to small bowel tumors, the most common type of appendiceal tumors are NETs with a reported frequency of 65%, followed by mucinous adenocarcinoma (10%), and signet ring and Goblet cell carcinoma (5%) [49–51]. The percentage of NETs of the appendix has increased over the last decade. This was documented by a Surveillance, Epidemiology and End Results (SEER) database analysis that included all patients with appendiceal malignancies diagnosed between 1973 and 2007. In this study, the incidence of appendiceal NETs was only 11% [52]. The incidence of NETs seems to be slightly higher in women [53, 54]. The average age at presentation of appendiceal cancer is approximately 63 years old for all types of appendiceal cancers except for NETs. These tumors tend to present earlier with a reported average age at diagnosis of approximately 42 years old [55].

Epithelial Tumors

This chapter will focus on appendiceal adenocarcinoma. Benign epithelial tumors can also arise in the appendix and include mucosal hyperplasia, simple cysts, mucinous cystadenomas, and mucinous cystadenocarcinomas. There is a certain degree of overlap between benign and malignant tumors, which has resulted in multiple attempts to classify appendiceal mucinous tumors over the years.

Appendiceal Adenocarcinoma

Most appendiceal adenocarcinomas are of mucinous subtype with at least 50% of the lesion composed of mucin. Most of these tumors arise from polyps or serrated adeno-

mas. Colonic-type appendiceal adenocarcinoma is the second most common histologic subtype [52, 56]. Some studies suggest a more invasive behavior in colonic subtype with a tendency to present with nodal metastasis, however, the evidence is conflicting [50, 57, 58]. The least common type is signet cell adenocarcinoma and carries a poor prognosis [52].

Clinical Presentation and Diagnosis

In contrast to NETs, incidental diagnosis of appendiceal adenocarcinoma is less common and the majority of patients (88%) present with acute appendicitis [58, 59]. Some patients are diagnosed incidentally while having surgery for an unrelated condition, but this has been reported in less than 20% of the cases [59].

Peritoneal Mucinous Carcinomatosis

Patients with mucinous subtype appendiceal adenocarcinoma may develop peritoneal metastasis leading to intraperitoneal accumulation of mucin. This condition is called peritoneal mucinous carcinomatosis and may cause abdominal discomfort, increased abdominal girth, and unexplained weight gain. Pseudomyxoma peritonei (PMP) is a term that for years has been used to refer to mucin accumulation due to excessive production by any tumor that produces mucin, including benign mucinous adenocarcinoma but also nonappendiceal mucinous neoplasms and benign mucinous tumors of the appendix. Multiple names and classifications have been proposed over the years in an attempt to differentiate mucinous appendiceal neoplasms according to the aggressiveness of their underlying histology (see Table 6.3) [60–67]. The lack of consensus in terminology creates barriers for the interpretation of data available and may create confusion regarding the prognosis of the patient. As of now, the lack of consensus remains, however, the Peritoneal Surface Oncology Group International (PSOGI) proposed a new classification for appendiceal mucinous neoplasms in 2015 (Table 6.4)

Table 6.3 Multiple histology-based categories have been proposed over the last 10 years for classification of appendiceal mucinous neoplasms [60–67]

Author	Classification categories
Ronnett et al. [60]	DPAM PMCA
Misdraji et al. [61]	LAMN MACA Discordant
Bradley et al. [62]	Low-grade mucinous carcinoma peritonei High-grade mucinous carcinoma peritonei
Pai et al. [63]	Mucinous adenoma Low-grade mucinous neoplasm with low risk of recurrence Low-grade mucinous neoplasm with low risk of recurrence with high risk of recurrence Mucinous adenocarcinoma
Carr et al. [64]	Adenoma Uncertain malignant potential Invasive mucinous adenocarcinoma
AJCC/WHO [65, 66]	Adenoma Invasive mucinous adenocarcinoma Low-grade mucinous adenocarcinoma High-grade mucinous adenocarcinoma
Carr et al. [67]	Adenoma, low or high-grade Serrated polyp, with or without dysplasia, low- or high-grade LAMN High-grade AMN Mucinous adenocarcinoma, well-, moderately, or poorly differentiated Poorly differentiated mucinous adenocarcinoma with signet ring cells Mucinous signet ring cell carcinoma

LAMN low-grade appendiceal mucinous neoplasm, *MCA* mucinous adenocarcinoma, *DPAM* disseminated peritoneal adenomucinosis, *PMCA* peritoneal mucinous carcinomatosis, *AJCC* American Joint Committee on Cancer, *WHO* world Health Organization, *AMN* appendiceal mucinous neoplasm

Table 6.4 Classification of appendiceal mucinous neoplasms

Terminology	Lesions
Tubular, tubulovillous or villous adenoma, low-grade or high-grade dysplasia	Adenoma resembling traditional colorectal type, confined to mucosa, muscularis mucosae intact
Serrated polyp with or without dysplasia	Tumor with serrated features confined to mucosa, muscularis mucosae intact
Low-grade appendiceal mucinous neoplasm (LAMN)	Mucinous neoplasm with low-grade cytologic atypia and any of the following: Loss of muscularis mucosae Fibrosis of submucosa Expansile or diverticulum-like growth Dissection of acellular mucin in wall Undulating or flattened epithelial growth Rupture of appendix Mucin and/or cells outside appendix
High-grade appendiceal mucinous neoplasm	Mucinous neoplasm with the architectural characteristics of LAMN and no infiltrative invasion, but with high-grade cytologic atypia
Mucinous adenocarcinoma—well, moderately, or poorly differentiated	Mucinous neoplasm with infiltrative invasion
Poorly differentiated (mucinous) adenocarcinoma with signet ring cells	Neoplasm with signet ring cells (< or = 50% of cells)
(Mucinous) signet ring cell carcinoma	Neoplasm with signet ring cells (>50% of cells)
Adenocarcinoma—well, moderately, or poorly differentiated	Nonmucinous adenocarcinoma resembling traditional colorectal type

Adapted from [67]

Table 6.5 Classification of pseudomyxoma peritonei (PMP) (peritoneal disease component)

Terminology	Lesions
Mucin without epithelial cells	Acellular mucin (A descriptive diagnosis followed by a comment is likely to be appropriate, depending on the overall clinical picture. It should be stated whether the mucin is confined to the vicinity of the organ of origin or distant from it; i.e., beyond the right lower quadrant in the case of the appendix. The term PMP should normally be avoided unless the clinical picture is characteristic.)
PMP with low-grade histologic features	Low-grade mucinous carcinoma peritonei or disseminated peritoneal adenomucinosis (DPAM)
PMP with high-grade histologic feature	High-grade mucinous carcinoma peritonei or peritoneal mucinous carcinomatosis (PMCA)
PMP with signet ring cells	High-grade mucinous carcinoma peritonei with signet ring cells or peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)

Adapted from [67]

[67]; the terminology was the result of a consensus of 71 experts from 13 different countries. This nomenclature is more extensive than previous ones and aims to end the long-standing confusion in terminology. It includes a nomenclature for appendiceal mucinous neoplasms (Table 6.4) and the term PMP was kept and subclassified (Table 6.5) [67].

Diagnosis is made by cross-sectional imaging followed by pathologic confirmation. CT scan of a patient with peritoneal mucinous carcinomatosis has some typical findings, such as low attenuation heterogeneous fluid throughout the peritoneum, scalloping of visceral surfaces, and scattered calcifications.

Staging and Prognosis

The 2017 AJCC TNM staging contains a specific staging for appendiceal carcinoma, which includes histologic grading for mucinous appendiceal neoplasms (see Table 6.6). Prognosis based on this version is not available but according to the seventh edition, the 5-year survival rate for patients with stage I disease was 81.1%, for stage II, 52.6%; for stage III, 32.9%; and for stage IV, 22.7%.

Histologic subtype is a major prognostic factor, with 5-year disease-specific survival of 58% for mucinous subtype, 55% for colonic subtype, and 27% for signet ring cell type [52]. However, as noted previously, mucinous subtype is a heterogeneous group and additional factors that affect prognosis include grade, cellularity, infiltrative invasion, and presence of signet ring cells.

Table 6.6 Appendiceal carcinoma TNM staging

Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intramucosal carcinoma; invasion of the lamina propria or extension into but not through the muscularis mucosae)
Tis(LAMN)	Low-grade appendiceal mucinous neoplasm confined by the muscularis propria. Acellular mucin or mucinous epithelium may invade into the muscularis propria T1 and T2 are not applicable to LAMN. Acellular mucin or mucinous epithelium that extends into the subserosa or serosa should be classified as T3 or T4a, respectively
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through muscularis propria into the subserosa or the mesoappendix
T4	Tumor penetrates the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and/or directly invades adjacent organs or structures
T4a	Tumor invades through the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or serosa of the mesoappendix
T4b	Tumor directly invades or adheres to adjacent organs or structures

Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph node measuring ≥ 0.2 mm) or any number of tumor deposits is present, and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa or mesentery
N2	Four or more regional lymph nodes are positive

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits
M1b	Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
M1c	Metastasis to sites other than peritoneum

Note: For specimens containing acellular mucin without identifiable tumor cells, efforts should be made to obtain additional tissue for thorough histologic examination to evaluate for cellularity

Table 6.6 (continued)

Histologic grade (G)	
G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

	AJCC prognostic stage groups			
When T is…	And N is…	And M is…	And grade is…	Then the stage group is…
Tis	N0	M0		0
Tis(LAMN)	N0	M0		0
T1	N0	M0		I
T2	N0	M0		I
T3	N0	M0		IIA
T4a	N0	M0		IIB
T4b	N0	M0		IIC
T1	N1	M0		IIIA
T2	N1	M0		IIIA
T3	N1	M0		IIIB
T4	N1	M0		IIIB
Any T	N2	M0		IIIC
Any T	N0	M1a		IVA
Any T	Any N	M1b	G1	IVA
Any T	Any N	M1b	G2, G3, or GX	IVB
Any T	Any N	M1c	Any G	IVC

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

Treatment

Early Stage Resectable Disease

The treatment of localized appendiceal adenocarcinoma is controversial, with conflicting findings regarding the advantage of hemicolectomy over appendectomy alone [68–70]. Some studies have found that hemicolectomy improves 5-year OS compared to appendectomy alone (73% vs. 44%), while no survival advantage was seen in a more recent study [57, 70]. Thus, management is highly variable according to institutional experience.

In low-grade mucinous tumors, adjuvant chemotherapy is not considered a standard of care approach. The use of adjuvant chemotherapy in high-grade appendiceal adenocarcinoma is extrapolated from the evidence available for colorectal adenocarcinoma, where efficacy of adjuvant 5-fluorouracil (5-FU)-based chemotherapy for node-positive colon cancer is well documented [57].

Metastatic Disease

There are no trials supporting the use of any particular chemotherapy in metastatic appendiceal adenocarcinoma, thus patients are usually treated following guidelines for colorectal adenocarcinoma.

Low-grade mucinous tumors usually metastasize to the peritoneal cavity. Hematogenous spread beyond the peritoneal cavity is very rare. Treatment for peritoneal mucinous carcinomatosis is aggressive cytoreduction and intraperitoneal hyperthermic chemotherapy (IPHC). This concept was evaluated in a trial of 105 patients with secondary peritoneal carcinomatosis from colon or appendiceal cancer and no other metastatic disease. Patients were randomized to IPHC with mitomycin plus debulking followed by systemic chemotherapy or systemic chemotherapy alone. Both groups received chemotherapy with weekly 5-FU and leucovorin until progression. Median survival was 22.4 months in patients receiving IPHC and debulking compared to 12.6 months in the control group [71]. Other institutions have reported similar favorable outcomes in [70, 72] with this regimen. A database review that included 103 patients with peritoneal mucinous carcinomatosis showed that adding IPHC to debulking surgery provided a survival advantage of 77 months vs. 25 months. Chemotherapy is usually reserved for patients where resection of peritoneal metastasis is no longer feasible.

Goblet Cell Carcinoid

Goblet cell carcinoid is a rare appendiceal tumor that expresses histologic characteristics of both colonic adenocarcinoma (e.g., CK20, immunoglobulin A (IgA) staining) and well-differentiated NETs (e.g., minimal atypia, rare mitotic figures) [73]. Based on histologic features of the primary tumor, goblet cell appendiceal malignancies are classified as goblet cell carcinoids (GCC) and atypical GCC. Atypical GCC is also known as adenocarcinoma ex GCC and is further divided into signet ring cell cancer (SRCC) and poorly differentiated appendiceal adenocarcinoid.

Clinical Presentation and Diagnosis

A SEER database analysis that included more than 2,000 patients with goblet cell malignancies found the median age at presentation was 54 years old in GCC and 57 years old in SRCC. Advance stage disease was reported to be more common at diagnosis in patients with SRCC compared to patients with GCC (61.4% vs. 10.4%). No difference in incidence according to gender or ethnicity was demonstrated [74].

Most patients present with appendicitis and less commonly with chronic lower abdominal pain, intussusception, or GI bleeding [50, 75]. The diagnosis is based on histology; no features in the clinical history or macroscopic findings in

the appendectomy specimen are suggestive of the diagnosis. The classic appearance of GCC has individual glands separated by smooth muscle cells and the lining cells contain intracytoplasmic mucin [76]. Urine 5-HIAA is not elevated in most cases.

Staging and Prognosis

GCCs behave more aggressively than well-differentiated NETs. There is no specific staging system for this histologic type of appendiceal cancer, thus they are staged similar to appendiceal carcinomas (see Table 6.6). Survival is better than in patients with appendiceal adenocarcinoma, but it is worse than with well-differentiated NETs [52]. Development of metastatic disease is reported to be more common in the elderly population and occurs in 15–30% of the cases [77]. Survival at 5 years according to stage is 100% for stage I, 76% for stage II, 22% for stage III, and 14% for stage IV [75]. There are very limited data regarding the prognosis of GCC according to the histologic subtype. A SEER database analysis of patients with appendiceal neoplasms included 1,582 patients with GCC and 534 patients with SRCC. This study reported a survival advantage for patients with GCC compared to SRCC regardless of their stage. The median OS (mOS) for atypical GCC was 24 months, while the median OS for GCC had not been reached at the time of analysis [74]. When adjusting for staging category (localized vs. advanced disease), the mOS was 35 months in localized SRCC and 15 months in patients with advances stages. The mOS was not reached for either of the staging subgroups among patients with GCC [74].

Treatment

There are only a few reports addressing treatment for GCC and expert recommendations vary for both early and advanced disease [78–82]. Most of these recommendations are extrapolated from other types of appendiceal cancers.

Localized Early Stage Disease

Surgery is recommended for patients who are surgical candidates and have localized disease; however, there is controversy regarding the extent of surgery. Some experts recommend simple appendectomy for localized low-grade tumors, whereas others recommend right colectomy for all goblet cell tumors [78, 79, 83]. Right colectomy has also been recommended based on criteria suggestive of poor prognosis such as tumor size > 2 cm, location in the base of the appendix, nodal involvement, and atypical GCC [80, 84]. Based on a SEER database analysis, SRCC tends to metastasize to regional lymph nodes regardless of primary tumor size; in addition, patients with SRCC showed improved survival in those who underwent surgery. Hence, a right colectomy is recommended in all SRCC patients with localized disease [74].

The benefit of using adjuvant therapy in these patients is not established and thus there are no guidelines available. Due to the more favorable outcome of early stage GCC patients, several experts recommend no adjuvant therapy unless high-risk features are present (i.e., cecal invasion, perforation, or lymph node involvement). On the other hand, since atypical GCC seems to have a higher tendency to metastasize to local lymph nodes, their recommendation is for adjuvant therapy in all patients with atypical GCC undergoing surgery.

Locally Advanced and Metastatic Disease

Systemic Treatment No clinical trials evaluating the role of chemotherapy in GCC are available. A case report of a patient with metastatic disease showed complete response (CR) with FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) treatment [81]. Expert recommendations are based on the reported outcomes for these tumors according to their histologic subclassification. For GCC with limited peritoneal disease options include peritoneal debulking plus hyperthermic intraperitoneal chemotherapy (HIPEC) or systemic chemotherapy with a fluorouracil-based regimen. For atypical GCC, fluorouracil-based chemotherapy is recommended as initial treatment with optional peritoneal resection in patients who respond well to the chemotherapy [74].

A small study reported that intraperitoneal disease commonly has characteristics of adenocarcinoma rather than carcinoid, thus aggressive management with debulking and HIPEC as described for appendiceal adenocarcinoma, may improve symptoms and OS [80]. This was a retrospective analysis of 45 patients with GCC treated with surgical debulking plus HIPEC that showed an OS of 63.4% at 3 years. Half of the patients in this study had regional lymph node involvement; however, no further subclassification (i.e., GCC vs. atypical GCC) was done [85].

References

1. Howlader NNA, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. Seer cancer statistics review, 1975–2012. Bethesda: National Cancer Institute; 2015. http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.
2. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249(1):63–71.
3. Overman MJ, Hu CY, Kopetz S, Abbruzzese JL, Wolff RA, Chang GJ. A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. Ann Surg Oncol. 2012;19(5):1439–45.

4. Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer. 2004;101(3):518–26.
5. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg. 2010;199(6):797–803.
6. Masselli G, Casciani E, Polettini E, Laghi F, Gualdi G. Magnetic resonance imaging of small bowel neoplasms. Cancer Imaging. 2013;13:92–9.
7. Laurent F, Raynaud M, Biset JM, Boisserie-Lacroix M, Grelet P, Drouillard J. Diagnosis and categorization of small bowel neoplasms: role of computed tomography. Gastrointest Radiol. 1991;16(2):115–9.
8. Miao F, Wang ML, Tang YH. New progress in CT and MRI examination and diagnosis of small intestinal tumors. World J Gastrointestinal Oncol. 2010;2(5):222–8.
9. Cronin CG, Scott J, Kambadakone A, Catalano OA, Sahani D, Blake MA, et al. Utility of positron emission tomography/CT in the evaluation of small bowel pathology. Br J Radiol. 2012;85(1017):1211–21.
10. Amin MBES, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. AJCC cancer staging manual. 8th ed. New York: Springer Nature; 2017.
11. Howe JR, Karnell LH, Menck HR, Scott-Conner C. The American College Of Surgeons Commission on cancer and the American Cancer Society. Adenocarcinoma of the small bowel: review of the national cancer data base, 1985–1995. Cancer. 1999;86(12):2693–706.
12. Sohn TA, Lillemoe KD, Cameron JL, Pitt HA, Kaufman HS, Hruban RH, et al. Adenocarcinoma of the duodenum: factors influencing long-term survival. J Gastrointest Surg. 1998;2(1):79–87.
13. Kaklamanos IG, Bathe OF, Franceschi D, Camarda C, Levi J, Livingstone AS. Extent of resection in the management of duodenal adenocarcinoma. Am J Surg. 2000;179(1):37–41.
14. Singhal N, Singhal D. Adjuvant chemotherapy for small intestine adenocarcinoma. Cochrane Database Syst Rev. 2007;2007(3):Cd005202.
15. Swartz MJ, Hughes MA, Frassica DA, Herman J, Yeo CJ, Riall TS, et al. Adjuvant concurrent chemoradiation for node-positive adenocarcinoma of the duodenum. Arch Surg. (Chicago, Ill: 1960). 2007;142(3):285–8.
16. Ouriel K, Adams JT. Adenocarcinoma of the small intestine. Am J Surg. 1984;147(1):66–71.
17. Czaykowski P, Hui D. Chemotherapy in small bowel adenocarcinoma: 10-year experience of the British Columbia Cancer Agency. Clin Oncol (R Coll Radiol). 2007;19(2):143–9.
18. Fishman PN, Pond GR, Moore MJ, Oza A, Burkes RL, Siu LL, et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. Am J Clin Oncol. 2006;29(3):225–31.
19. Overman MJ, Kopetz S, Wen S, Hoff PM, Fogelman D, Morris J, et al. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. Cancer. 2008;113(8):2038–45.
20. Zaanan A, Gauthier M, Malka D, Locher C, Gornet JM, Thirot-Bidault A, et al. Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (folfiri regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter ageo study. Cancer. 2011;117(7):1422–8.
21. Santini D, Fratto ME, Spoto C, Russo A, Galluzzo S, Zoccoli A, et al. Cetuximab in small bowel adenocarcinoma: a new friend? Br J Cancer. 2010;103(8):1305; author reply 1306.
22. Tsang H, Yau T, Khong PL, Epstein RJ. Bevacizumab-based therapy for advanced small bowel adenocarcinoma. Gut. 2008;57(11):1631–2.
23. Ruemmele P, Dietmaier W, Terracciano L, Tornillo L, Bataille F, Kaiser A, et al. Histopathologic features and microsatellite instability of cancers of the papilla of vater and their precursor lesions. Am J Surg Pathol. 2009;33(5):691–704.
24. Howe JR, Klimstra DS, Cordon-Cardo C, Paty PB, Park PY, Brennan MF. K-ras mutation in adenomas and carcinomas of the ampulla of vater. Clin Cancer Res. 1997;3(1):129–33.
25. Kadmon M, Tandara A, Herfarth C. Duodenal adenomatosis in familial adenomatous polyposis coli. A review of the literature and results from the heidelberg polyposis register. Int J Color Dis. 2001;16(2):63–75.
26. Benhamiche AM, Jouve JL, Manfredi S, Prost P, Isambert N, Faivre J. Cancer of the ampulla of vater: results of a 20-year population-based study. Eur J Gastroenterol Hepatol. 2000;12(1):75–9.
27. Palazzo L. Staging of ampullary carcinoma by endoscopic ultrasonography. Endoscopy. 1998;30(Suppl 1):A128–31.
28. Talamini MA, Moesinger RC, Pitt HA, Sohn TA, Hruban RH, Lillemoe KD, et al. Adenocarcinoma of the ampulla of vater. A 28-year experience. Ann Surg. 1997;225(5):590–9; discussion 599–600.
29. O'Connell JB, Maggard MA, Manunga J Jr, Tomlinson JS, Reber HA, Ko CY, et al. Survival after resection of ampullary carcinoma: a national population-based study. Ann Surg Oncol. 2008;15(7):1820–7.
30. Quirk DM, Rattner DW, Fernandez-del Castillo C, Warshaw AL, Brugge WR. The use of endoscopic ultrasonography to reduce the cost of treating ampullary tumors. Gastrointest Endosc. 1997;46(4):334–7.
31. Monson JR, Donohue JH, McEntee GP, McIlrath DC, van Heerden JA, Shorter RG, et al. Radical resection for carcinoma of the ampulla of vater. Arch Surg. (Chicago, Ill: 1960). 1991;126(3):353–7.
32. Tsukada K, Takada T, Miyazaki M, Miyakawa S, Nagino M, Kondo S, et al. Diagnosis of biliary tract and ampullary carcinomas. J Hepato-Biliary-Pancreat Surg. 2008;15(1):31–40.
33. Yamaguchi K, Enjoji M, Tsuneyoshi M. Pancreatoduodenal carcinoma: a clinicopathologic study of 304 patients and immunohistochemical observation for cea and ca19-9. J Surg Oncol. 1991;47(3):148–54.
34. Beger HG, Treitschke F, Gansauge F, Harada N, Hiki N, Mattfeldt T. Tumor of the ampulla of vater: experience with local or radical resection in 171 consecutively treated patients. Arch Surg. (Chicago, Ill: 1960). 1999;134(5):526–32.
35. Allema JH, Reinders ME, van Gulik TM, van Leeuwen DJ, Verbeek PC, de Wit LT, et al. Results of pancreaticoduodenectomy for ampullary carcinoma and analysis of prognostic factors for survival. Surgery. 1995;117(3):247–53.
36. Chang DK, Jamieson NB, Johns AL, Scarlett CJ, Pajic M, Chou A, et al. Histomolecular phenotypes and outcome in adenocarcinoma of the ampulla of vater. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(10):1348–56.
37. Shaib WL, Sharma R, Brutcher E, Kim S, Maithel SK, Chen Z, et al. Treatment utilization and surgical outcome of ampullary and duodenal adenocarcinoma. J Surg Oncol. 2014;109(6):556–60.
38. Kamisawa T, Tu Y, Egawa N, Nakajima H, Horiguchi S, Tsuruta K, et al. Clinicopathologic features of ampullary carcinoma without jaundice. J Clin Gastroenterol. 2006;40(2):162–6.
39. Todoroki T, Koike N, Morishita Y, Kawamoto T, Ohkohchi N, Shoda J, et al. Patterns and predictors of failure after curative resections of carcinoma of the ampulla of vater. Ann Surg Oncol. 2003;10(10):1176–83.
40. Yao HS, Wang Q, Wang WJ, Hu ZQ. Intraoperative allogeneic red blood cell transfusion in ampullary cancer outcome after curative pancreatoduodenectomy: a clinical study and meta-analysis. World J Surg. 2008;32(9):2038–46.
41. Duffy JP, Hines OJ, Liu JH, Ko CY, Cortina G, Isacoff WH, et al. Improved survival for adenocarcinoma of the ampulla of vater:

fifty-five consecutive resections. Arch Surg. 2003;138(9):941–8; Discussion 948–950.
42. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periampullary adenocarcinoma: analysis of 5-year survivors. Ann Surg. 1998;227(6):821–31.
43. Bhatia S, Miller RC, Haddock MG, Donohue JH, Krishnan S. Adjuvant therapy for ampullary carcinomas: the Mayo Clinic experience. Int J Radiat Oncol Biol Phys. 2006;66(2):514–9.
44. Sikora SS, Balachandran P, Dimri K, Rastogi N, Kumar A, Saxena R, et al. Adjuvant chemo-radiotherapy in ampullary cancers. Eur J Surg Oncol. 2005;31(2):158–63.
45. Zhou J, Hsu CC, Winter JM, Pawlik TM, Laheru D, Hughes MA, et al. Adjuvant chemoradiation versus surgery alone for adenocarcinoma of the ampulla of vater. Radiother Oncol. 2009;92(2):244–8.
46. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the espac-3 periampullary cancer randomized trial. JAMA. 2012;308(2):147–56.
47. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200–10.
48. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267–77.
49. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum. 1998;41(1):75–80.
50. McCusker ME, Cote TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. Cancer. 2002;94(12):3307–12.
51. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. Eur J Surg Oncol. 2008;34(2):196–201.
52. Turaga KK, Pappas SG, Gamblin T. Importance of histologic subtype in the staging of appendiceal tumors. Ann Surg Oncol. 2012;19(5):1379–85.
53. Shaib WL, Goodman M, Chen Z, Kim S, Brutcher E, Bekaii-Saab T, et al. Incidence and survival of appendiceal mucinous neoplasms: a SEER analysis. Am J Clin Oncol. 2017;22(9):1107–16.
54. Overman MJ, Fournier K, Hu CY, Eng C, Taggart M, Royal R, et al. Improving the ajcc/tnm staging for adenocarcinomas of the appendix: the prognostic impact of histological grade. Ann Surg. 2013;257(6):1072–8.
55. Sandor A, Modlin IM. A retrospective analysis of 1570 appendiceal carcinoids. Am J Gastroenterol. 1998;93(3):422–8.
56. Kabbani W, Houlihan PS, Luthra R, Hamilton SR, Rashid A. Mucinous and nonmucinous appendiceal adenocarcinomas: different clinicopathological features but similar genetic alterations. Mod Pathol. 2002;15(6):599–605.
57. Nitecki SS, Wolff BG, Schlinkert R, Sarr MG. The natural history of surgically treated primary adenocarcinoma of the appendix. Ann Surg. 1994;219(1):51–7.
58. Ito H, Osteen RT, Bleday R, Zinner MJ, Ashley SW, Whang EE. Appendiceal adenocarcinoma: long-term outcomes after surgical therapy. Dis Colon Rectum. 2004;47(4):474–80.
59. Cerame MA. A 25-year review of adenocarcinoma of the appendix. A frequently perforating carcinoma. Dis Colon Rectum. 1988;31(2):145–50.
60. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol. 1995;19(12):1390–408.
61. Misdraji J, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. Am J Surg Pathol. 2003;27(8):1089–103.
62. Bradley RF, JHt S, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol. 2006;30(5):551–9.
63. Pai RK, Beck AH, Norton JA, Longacre TA. Appendiceal mucinous neoplasms: clinicopathologic study of 116 cases with analysis of factors predicting recurrence. Am J Surg Pathol. 2009;33(10):1425–39.
64. Carr NJSL, Adenocarcinoma of the appendix. WHO classification of tumours of the digestive system. 4th ed. Lyon: IRAC Press; 2010. p. 122–8.
65. Edge SBBD, Compton CC, Fritz AG, Greene FL, Trotti A III, editors. Ajcc cancer staging manual. 7th ed. New York: Springer; 2010.
66. Bosman FTCF, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. New York: IARC; 2010.
67. Carr NJ, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, Gonzalez-Moreno S, et al. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia: the results of the peritoneal surface oncology group international (psogi) modified delphi process. Am J Surg Pathol. 2016;40(1):14–26.
68. Hartley JE, Drew PJ, Qureshi A, MacDonald A, Monson JR. Primary adenocarcinoma of the appendix. J R Soc Med. 1996;89(2):111p–3p.
69. Ferro M, Anthony PP. Adenocarcinoma of the appendix. Dis Colon Rectum. 1985;28(6):457–9.
70. Gonzalez-Moreno S, Sugarbaker PH. Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. Br J Surg. 2004;91(3):304–11.
71. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2003;21(20):3737–43.
72. Chua TC, Al-Alem I, Saxena A, Liauw W, Morris DL. Surgical cytoreduction and survival in appendiceal cancer peritoneal carcinomatosis: an evaluation of 46 consecutive patients. Ann Surg Oncol. 2011;18(6):1540–6.
73. Kanthan R, Saxena A, Kanthan SC. Goblet cell carcinoids of the appendix: immunophenotype and ultrastructural study. Arch Pathol Lab Med. 2001;125(3):386–90.
74. Shaib W, Krishna K, Kim S, Goodman M, Rock J, Chen Z, et al. Appendiceal neuroendocrine, goblet and signet-ring cell tumors: a spectrum of diseases with different patterns of presentation and outcome. Cancer Res Treat. 2016;48(2):596–604.
75. Pham TH, Wolff B, Abraham SC, Drelichman E. Surgical and chemotherapy treatment outcomes of goblet cell carcinoid: a tertiary cancer center experience. Ann Surg Oncol. 2006;13(3):370–6.
76. Burke AP, Sobin LH, Federspiel BH, Shekitka KM, Helwig EB. Goblet cell carcinoids and related tumors of the vermiform appendix. Am J Clin Pathol. 1990;94(1):27–35.
77. Gallegos NC, Milroy C, Linehan IP, Boulos PB. Crypt cell carcinoma of the appendix. Eur J Surg Oncol. 1992;18(4):386–7.
78. Varisco B, McAlvin B, Dias J, Franga D. Adenocarcinoid of the appendix: is right hemicolectomy necessary? A meta-analysis of retrospective chart reviews. Am Surg. 2004;70(7):593–9.

79. Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, et al. Enets consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology. 2012;95(2):135–56.
80. Butler JA, Houshiar A, Lin F, Wilson SE. Goblet cell carcinoid of the appendix. Am J Surg. 1994;168(6):685–7.
81. Garin L, Corbinais S, Boucher E, Blanchot J, Le Guilcher P, Raoul JL. Adenocarcinoid of the appendix vermiformis: complete and persistent remission after chemotherapy (folfox) of a metastatic case. Dig Dis Sci. 2002;47(12):2760–2.
82. Lin BT, Gown AM. Mixed carcinoid and adenocarcinoma of the appendix: report of 4 cases with immunohistochemical studies and a review of the literature. Appl Immunohistochem Mol Morphol. 2004;12(3):271–6.
83. Boudreaux JP, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, et al. The nanets consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas. 2010;39(6):753–66.
84. Byrn JC, Wang JL, Divino CM, Nguyen SQ, Warner RR. Management of goblet cell carcinoid. J Surg Oncol. 2006;94(5):396–402.
85. McConnell YJ, Mack LA, Gui X, Carr NJ, Sideris L, Temple WJ, et al. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: an emerging treatment option for advanced goblet cell tumors of the appendix. Ann Surg Oncol. 2014;21(6):1975–82.

Adjuvant Therapy for Colorectal Cancer

7

Patrick Boland, Jun Gong, and Marwan Fakih

Introduction

Despite the advances achieved in colorectal cancer screening and the persistent decline in the incidence and mortality of colorectal cancer, colorectal cancer continues to represent the second most common cause of cancer death in the United States. It is estimated that 138,000 cases of colorectal cancer were diagnosed, of which 50,000 patients succumbed to advanced disease in 2014 [1]. While significant progress has been made in the management of metastatic colorectal cancer in terms of improved longevity, metastatic disease remains largely noncurable with a median survival of 30 months or less [2]. Therefore, the most effective strategies in decreasing colorectal death have to focus on disease prevention, early detection, and improvements in adjuvant therapies. This chapter will focus on the historical and recent advances in adjuvant therapy for locoregional colorectal cancer and following resection of metastatic disease.

Adjuvant Therapy for Colon Cancer

Adjuvant therapy remains universally recommended for stage III colon cancer. Over the past three decades, the development of adjuvant therapy with fluoropyrimidines has reduced the risk of recurrence and afforded an absolute survival benefit of 10–15% in stage III colon cancer [3]. The addition of oxaliplatin to fluoropyrimidine-based adjuvant therapy offers an additional 4–6% absolute survival benefit. In contrast, the benefit of adjuvant chemotherapy in stage II disease remains under debate. At best, adjuvant chemotherapy in stage II colon cancer appears to provide no more than a 5% absolute improvement in 5-year survival. Currently, adjuvant therapy is not recommended in stage I colon cancer, given the favorable prognosis and high probability of cure with surgery alone in this group. In this section, we detail the development of adjuvant therapy in stage II and III colon cancer from which current guidelines stem.

Stage I Colon Cancer

Approximately 21% of all colon cancer cases are accounted for by stage I disease [4]. The 5-year disease-specific survival (DSS) rate for stage I colon cancer is about 95% [5]. The 5-year overall survival (OS) rate in patients with stage I disease treated with surgery alone remains favorable and is at least 80–90% [6]. Given the very favorable prognosis and high rates of curative resection, the risk–benefit ratio for currently available adjuvant chemotherapy favors no further treatment beyond surgery in stage I colon cancer at present [6].

Stage III Colon Cancer

Stage III disease accounts for approximately 20–25% of all cases of colon cancer [4]. Roughly 15% of patients have stage IIIB colon cancer, 5% have stage IIIC disease, and 3% have stage IIIA disease. The 5-year DSS and OS rates for stage III colon cancer are approximately 68.7% and 58.3%, respectively [5]. For stage IIIA, stage IIIB, and stage IIIC disease, 5-year DSS rates are 89%, 70.4%, and 55.8%, respectively, and 5-year OS rates are 79%, 59%, and 47.9%, respectively. The development of adjuvant therapy over the past three decades has reduced the risk of recurrence and improved survival in stage III colon cancer [1].

P. Boland
Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

J. Gong
Division of Medical Oncology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

M. Fakih (✉)
Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA
e-mail: mfakih@coh.org

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_7

Table 7.1 Phase 3 adjuvant therapy trials with 5-fluorouracil in stage III colon cancer

Study	*n* = size	Arms	DFS[a]	OS[a]
INT-0035 [8]	929	Levamisole vs. observation Levamisole + 5-FU vs. observation	2% ↓ recurrence rate ($p = 0.86$) 40% ↓ recurrence rate ($p < 0.0001$)	6% ↓ death rate ($p = 0.57$) 33% ↓ death rate ($p = 0.0007$)
NSABP C-03 [9]	1081	5-FU/LV vs. MOF	66% vs. 54% ($p = 0.0004$)	76% vs. 66% ($p = 0.003$)
NSABP C-04 [10]	2151	5-FU/LV vs. 5-FU/LEV 5-FU/LV vs. 5-FU/LV/LEV	65% vs. 60% ($p = 0.04$) 65% vs. 64% ($p = 0.67$)	74% vs. 70% ($p = 0.07$) 74% vs. 73% ($p = 0.99$)
adjCCA-01 [11]	680	5-FU/LV 5-FU/LEV	79.8 months 69.3 months ($p = 0.012$)	88.9 months 78.6 months ($p = 0.003$)
INT-0089 [12]	3561	LDLV HDLV 5-FU + LEV LDLV + LEV	10-year 49% 10-year 47% 10-year 45% 10-year 68%[b]	10-year 52% 10-year 52% 10-year 50% 10-year 59%[b]
NSABP C-06 [13]	1608	UFT/LV vs. 5-FU/LV	HR 1.004 (95% CI 0.847–1.190, $p = 0.96$)	HR 1.014 (95% CI 0.825–1.246, $p = 0.90$)
X-ACT [14]	1987	Capecitabine vs. 5-FU/LV	3.8 years, HR 0.87 (95% CI 0.75–1.00, $p = 0.05$)	3.8 years, HR 0.84 (95% CI 0.69–1.01, $p = 0.07$)

DFS disease-free survival, *OS* overall survival, *5-FU* 5-fluorouracil, *LV* leucovorin, *MOF* semustine + vincristine + 5-FU, *LEV* levamisole, *LDLV* low-dose LV + 5-FU (Mayo Clinic regimen), *HDLV* high-dose LV + 5-FU (Roswell Park regimen), *UFT* uracil + tegafur, *HR* hazard ratio, *CI* confidence interval

[a]5 years unless otherwise specified

[b]*p*-values not reported but not statistically significant across all arms

Adjuvant Therapy with Fluoropyrimidine

Early randomized studies (as early as the 1950s) largely failed to demonstrate an unequivocal benefit for adjuvant chemotherapy in colorectal cancer [7]. Analysis of various regimens during this period identified, at best, a significant but marginal improvement in 5-year OS by a few percentage points with adjuvant fluorouracil or fluorouracil-containing chemotherapy. These investigations were felt to be limited by insufficient numbers of study patients and suboptimal adherence to chemotherapy. Later and better-conducted randomized studies have shown that adjuvant 5-fluorouracil (5-FU) does improve outcomes in stage III colon cancer (Table 7.1) [8–14].

In 1987, the North Central Cancer Treatment Group (NCCTG), Eastern Cooperative Oncology Group (ECOG), and Southwest Oncology Group (SWOG) completed enrollment of their phase III trial (Intergroup 0035 or INT-0035) investigating observation vs. levamisole alone (50 mg orally three times daily for 3 days every 2 weeks for 1 year) vs. levamisole + 5-FU (450 mg/m^2 intravenous [IV] daily for 5 days followed by weekly IV 5-FU 450 mg/m^2 28 days later for 48 weeks) in patients who had received curative-intent resections of stage III colon cancer in the prior 1–5 weeks [8]. Although adjuvant levamisole + 5-FU failed to demonstrate outcome differences in stage II disease, 929 patients with stage III disease followed ≥5 years receiving adjuvant levamisole + 5-FU experienced a 40% reduction in recurrence rate vs. postsurgical observation ($p < 0.0001$) and a 33% reduction in mortality rate vs. observation ($p = 0.0007$). Adverse effects (AEs) were primarily of those expected for bolus 5-FU: nausea, vomiting, stomatitis, diarrhea, dermatitis, fatigue, alopecia, mild leukopenia, and grade 1–2 thrombocytopenia. These data had a positive influence at the time of a National Institutes of Health (NIH) consensus development panel in 1990 that recommended postoperative levamisole + 5-FU in patients with stage III colon cancer unable to enroll in a clinical trial [6].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) investigators similarly conducted a series of large randomized trials involving adjuvant fluorouracil in colon cancer [15]. NSABP protocol C-01 compared semustine (MeCCNU) + vincristine + 5-FU (MOF) or bacillus Calmette–Guérin (BCG) to observation in 1166 patients with resected stage II or III disease. Although adjuvant MOF produced improved disease-free survival (DFS) and OS at 5 years compared to postoperative observation, these results disappeared at 10-year follow-up [16]. NSABP protocol C-02 did produce improved 5-year DFS rates with perioperative portal vein infusion of 5-FU (69%) vs. surgery only (60%, $p = 0.02$) in 1158 patients with resected stage II or III colon cancer, but did not produce a significant OS benefit [17]. Furthermore, the development of more effective IV chemotherapies with 5-FU favored the use of IV chemotherapy over portal venous infusion 5-FU in later NSABP studies.

NSABP protocol C-03 compared adjuvant 5-FU (500 mg/m^2 IV bolus 1 hour after leucovorin [LV] infusion weekly for 6 doses = 1 cycle) + LV (500 mg/m^2 2-hour IV infusion weekly for 6 doses, Roswell Park regimen) for 8 cycles to the methyl-CCNU, vincristine, and fluorouracil (MOF) regimen from NSABP protocol C-01 and showed a superior 5-year DFS rate (66%) and OS rate (76%) in the 5-FU/LV arm vs. MOF arm (5-year DFS rate of 54% [$p = 0.0004$] and OS rate of 66% [$p = 0.003$]) in patients with stage II or III disease.

5-FU/LV therapy had a similar rate of ≥ grade 4 AEs (6%) compared to MOF but less hematologic toxicities (0.8% vs. 16% with white blood cell [WBC] count <2000/μ[mu]L and none vs. 15% with platelets <50,000/μ[mu]L) than MOF [9]. MOF notably had more cases of myeloproliferative disorder and leukemia than 5-FU/LV, but 5-FU/LV had more diarrhea (85%) than MOF (48%). Of note, 5-FU/LV became the control for later NSABP trials. The stage was set for adjuvant 5-FU/LV vs. 5-FU/levamisole (LEV) in NSABP protocol C-04 when 5-FU/LV in six 8-week cycles (Roswell Park regimen, 2 weeks of rest), 5-FU/LEV (INT-0035 similar dosing scheme), or 5-FU/LV/LEV was administered in patients with resected stage II or III colon cancer [10]. Fluorouracil/LV showed improved 5-year DFS rates (65%) vs. 5-FU/LEV (60%, $p = 0.04$) and slightly prolonged OS rates (74%) vs. 5-FU/LEV (70%, $p = 0.07$). Notably, 5-FU/LV/LEV did not provide any DFS (64%) or OS (73%) benefit over 5-FU/LV alone (5-year DFS of 65% ($p = 0.67$) and OS of 74% ($p = 0.99$)). Grade 3–4 toxicity rates were comparable across arms, while diarrhea was the major AE in LV-containing arms and stomatitis rates were higher in the 5-FU/LEV arm. In stage III disease only, adjuvant low-dose LV + 5-FU (100 mg/m^2 LV + 450 mg/m^2 5-FU IV daily for 5 days every 4 weeks) has shown superiority over 5-FU/LEV (INT-0035 similar dosing) albeit over 12 months in the adjCCA-01 trial [11]. These results supported 5-FU/LV as an acceptable adjuvant therapeutic standard in colon cancer.

The Intergroup 0089 (INT-0089) separately investigated high-dose LV + 5-FU (HDLV or Roswell Park regimen) for 4 cycles vs. low-dose LV + 5-FU (20 mg/m^2 LV and 425 mg/m^2 5-FU IV daily for 5 days repeated at 4 weeks, 8 weeks, and every 5 weeks) for 6 cycles (LDLV or Mayo Clinic regimen) vs. LDLV + LEV (50 mg orally three times daily for 3 days every 2 weeks for 6 months) vs. 5-FU + LEV (INT-0035 regimen) in >3500 patients with resected high-risk stage II (defined as evidence of bowel obstruction or perforation or adherence to or invasion of adjacent organs or tumor perforation) or stage III colon cancer [12]. None of these four treatment arms demonstrated statistical superiority over another in 10-year DFS and OS though ≥ grade 3 toxicities were more frequent in the LDLV and LDLV + LEV arms. The HDLV arm was not significantly different in overall toxicity from the 5-FU + LEV arm though 5-FU + LEV had more neurologic AEs, and the LDLV + LEV arm was more significantly toxic than the LDLV arm. Of note, infusional 5-FU has not demonstrated significantly improved survival outcomes compared to bolus 5-FU in the adjuvant treatment of stage III colon cancer, but infusional 5-FU appears to be generally more tolerated and less toxic [18, 19]. In short, INT-0089 highlighted that adjuvant LDLV or HDLV could derive similar survival benefits with 6–8 months of therapy, instead of 12 months, without the additional toxicity of levamisole.

Oral fluoropyrimidines have also been investigated in the adjuvant setting for stage III disease (Table 7.1). NSABP protocol C-06 pitted 5-FU/LV (Roswell Park regimen) vs. uracil and tegafur (UFT, 300 mg/m^2 oral daily for 4 weeks with 1 week off = 1 cycle) + LV (90 mg oral daily for 4 weeks) for 5 cycles in those with stage II or III disease having undergone curative-intent resection in the past 42 days [13]. Adjuvant UFT/LV showed equivalent efficacy to 5-FU/LV with a 5-year DFS hazard ratio (HR) of 1.004 (95% confidence interval [CI] 0.847–1.190, $p = 0.96$) and OS HR of 1.014 (95% CI 0.825–1.246, $p = 0.90$). UFT/LV also showed similar toxicity to 5-FU/LV with diarrhea being the most common AE in both (28.5% ≥ grade 3 diarrhea and 37.8% ≥ grade 3 any toxicity for UFT/LV vs. 29.4% ≥ grade 3 diarrhea and 38.2% ≥ grade 3 any toxicity for 5-FU/LV). The Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial compared capecitabine (1250 mg/m^2 oral twice daily days 1–14 every 21 days) for 8 cycles to 5-FU/LV (Mayo Clinic regimen) for 6 cycles in stage III colon cancer and showed that adjuvant capecitabine is at least as equivalent in 3.8-year DFS and OS, improved relapse-free survival or RFS (HR 0.86, 95% CI 0.74–0.99, $p = 0.04$), and had significantly fewer ≥ grade 3 AEs (except for hand–foot syndrome) compared to 5-FU/LV [14].

In summary, large randomized trials within the past 30 years have demonstrated that adjuvant therapy with fluoropyrimidines improves survival in stage III colon cancer. Furthermore, 6 months of treatment with 5-FU/LV or capecitabine has been well-established as a standard adjuvant chemotherapy in stage III disease. Infusional 5-FU/LV (de Gramont regimen) or capecitabine appears to be more favorable in terms of toxicity than bolus 5-FU/LV regimens and is typically favored when fluoropyrimidine monotherapy is considered.

Adjuvant Therapy with Fluoropyrimidine and Oxaliplatin

From 1998 to 2001, the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) phase III trial randomized 2246 patients to receive 6 months of biweekly 5-FU/LV or LV5FU2 (200 mg/m^2 LV 2-hour IV infusion followed by 400 mg/m^2 5-FU IV bolus then 600 mg/m^2 5-FU 22-hour IV infusion every 14 days) vs. 6 months of oxaliplatin (85 mg/m^2 2-hour IV infusion on day 1) + LV5FU2 (FOLFOX4) within 7 weeks of complete resection of stage II or III colon cancer [20]. Although FOLFOX4 had more grade 3–4 neutropenia (41.1% vs. 4.7%, $p < 0.001$) and neuropathy (48.2% grade 1), the DFS at 3 years was significantly improved in the FOLFOX4 arm (78.2%, 95% CI 75.6–80.7%) vs. LV5FU2 arm (72.9%, 95% CI 70.2–75.7%, $p = 0.002$), and the risk of relapse was reduced by 23% in the FOLFOX4 arm when compared to the LV5FU2 arm (HR

0.77, $p = 0.002$). Survival benefits of adjuvant FOLFOX4 have been observed at 10-year follow-up (Table 7.2 [20–24]) though the DFS and OS benefits appear to be restricted to stage III disease [21].

In 2000, the NSABP investigators launched a parallel phase III trial (NSABP protocol C-07) pitting 6 months of 5-FU/LV (Roswell Park regimen) vs. 6 months of FLOX (5-FU/LV Roswell Park regimen + oxaliplatin 85 mg/m^2 2-hour IV infusion on days 1, 15, and 29) in resected stage II or III disease (within 42 days) [22]. At 5-year follow-up, FLOX remained superior to 5-FU/LV in DFS (HR 0.82, 95% CI 0.72–0.93, $p = 0.002$), but OS was similar in both arms (HR 0.88, 95% CI 0.75–1.02, $p = 0.08$) [23]. Notably, significantly more cases of grade 3–4 diarrhea ($p = 0.003$), bowel wall injury in the elderly (age > 60 years, $p < 0.01$) and females ($p < 0.01$), febrile neutropenia or bacteremia associated with diarrhea ($p = 0.01$), grade 3–4 nausea/vomiting ($p < 0.001$), grade 3–4 neuropathy ($p < 0.001$), and death from chemotherapy-induced enteropathy (5 deaths vs. 1 death) were seen in the FLOX arm vs. the 5-FU/LV arm.

More recently, the NO16968 multinational phase III trial investigated bolus 5-FU/LV (Mayo Clinic regimen, 6 cycles or Roswell Park regimen, 4 cycles) vs. capecitabine (1000 mg/m^2 oral twice daily days 1–14 every 3 weeks) + oxaliplatin (130 mg/m^2 2-hour IV infusion on day 1) for 8 cycles (XELOX) in patients who had undergone curative-intent resections of stage III disease in the prior 8 weeks [24]. XELOX demonstrated superior DFS rates at 7 years vs. bolus 5-FU/LV (HR 0.80, 95% CI 0.69–0.93, $p = 0.004$) and OS rates at 7 years vs. bolus 5-FU/LV (HR 0.83, 95% CI 0.70–0.99, $p = 0.04$). The XELOX arm experienced more grade 3–4 neuropathy, grade 3 hand–foot syndrome, and grade 3–4 thrombocytopenia, but less grade 3–4 neutropenia, febrile neutropenia, and stomatitis than the bolus 5-FU/LV arm.

The results of these three major trials highlight that the addition of oxaliplatin to 5-FU/LV (continuous infusion or bolus) in the adjuvant setting reduces the relative risk of relapse and relative risk of death by up to 21% and 20%, respectively, compared to standard 5-FU/LV alone and have redefined the standard adjuvant chemotherapy in stage III colon cancer. Accordingly, following the findings of the MOSIAC trial, the US Food and Drug Administration (FDA) in 2004 approved FOLFOX4 for the adjuvant treatment of patients with stage III colon cancer. Findings from the NO16968 study support adjuvant XELOX as an acceptable alternative to FOLFOX4 in stage III disease. Adjuvant FLOX, while effective in reducing relapses in comparison to fluoropyrimidines alone, should be avoided if possible due to an unacceptable rate of grade 3–4 gastrointestinal toxicities.

Adjuvant Therapy with 5-Fluorouracil and Irinotecan

In contrast to the survival benefits offered by adjuvant FOLFOX4 in stage III colon cancer, three major clinical trials on adjuvant therapy incorporating irinotecan with 5-FU/LV (FOLFIRI or IFL) have produced negative results in this arena (Table 7.3) [25–27]. In short, data from the Pan European Trial Adjuvant Colon Cancer (PETACC)-3, FNCLCC Accord02/FFCD9802, and Cancer and Leukemia

Table 7.2 Phase 3 adjuvant therapy trials with 5-fluorouracil and oxaliplatin in stage III colon cancer

Study	*n* = size	Arms	DFS[a]	OS[a]
MOSAIC [20, 21]	2246	FOLFOX4 vs. LV5FU2	10-year 62.2% vs. 53.8% (HR 0.79, 95% CI 67–94%, $p = 0.007$)	10-year 67.1% vs. 59.0% (HR 0.80, 95% CI 66–96%, $p = 0.016$)
NSABP C-07 [22, 23]	2409	FLOX vs. 5-FU/LV (RP)	69.4% vs. 64.2% (HR 0.82, 95% CI 0.72–0.93, $p = 0.002$)	80.2% vs. 78.4% (HR 0.88, 95% CI 0.75–1.02, $p = 0.08$)
NO16968 [24]	1886	XELOX vs. 5-FU/LV (MC or RP)	7-year 63% vs. 56% (HR 0.80, 95% CI 0.69–0.93, $p = 0.004$)	7-year 73% vs. 67% (HR 0.83, 95% CI 0.70–0.99, $p = 0.04$)

DFS disease-free survival, *OS* overall survival, *5-FU* 5-fluorouracil, *LV* leucovorin, *FOLFOX* 5-FU + LV + oxaliplatin, *LV5FU2* biweekly 5-FU/LV, *HR* hazard ratio, *CI* confidence interval, *FLOX* 5-FU/LV (Roswell Park regimen) + oxaliplatin, *RP* Roswell Park regimen, *XELOX* capecitabine + oxaliplatin, *MC* Mayo Clinic regimen

[a]5-year unless otherwise specified

Table 7.3 Phase III adjuvant therapy trials with 5-fluorouracil and irinotecan in stage III colon cancer

Study	*n* = size	Arms	DFS[a]	OS[a]
CALGB 89803 [25]	1264	IFL vs. 5-FU/LV (RP)	59% (95% CI 55–63%) vs. 61% (95% CI 57–65%, p = 0.85)	68% (95% CI 64–72%) vs. 71% (95% CI 67–75%, $p = 0.74$)
PETACC-3 [26]	3278	FOLFIRI vs. LV5FU2	56.7% vs. 54.3% ($p = 0.106$)	73.6% vs. 71.3% ($p = 0.094$)
Accord02/FFCD9802 [27]	400	FOLFIRI vs. LV5FU2	3-year 51% vs. 60% (HR 1.12, 95% CI 0.85–1.47, $p = 0.42$)	61% vs. 67% (HR 1.00, 95% CI 0.71–1.40, $p = 0.99$)

DFS disease-free survival, *OS* overall survival, *5-FU* 5-fluorouracil, *LV* leucovorin, *IFL* irinotecan + bolus 5-FU/LV, *RP* Roswell Park regimen, *CI* confidence interval, *FOLFIRI* LV5FU2 + irinotecan, *LV5FU2* biweekly 5-FU/LV, *HR* hazard ratio

[a]5-year unless otherwise specified

Group B (CALGB) 89,803 phase III trials do not support a role for adjuvant irinotecan with 5-FU/LV in stage III disease [25–27].

Adjuvant Therapy with Targeted Agents in Colon Cancer

Several randomized clinical trials have investigated the addition of biologic therapies that target vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR) in the adjuvant treatment of stage II and III colon cancer. NSABP protocol C-08 randomized 2710 patients with stage II or III disease to receive 12 cycles (6 months) of modified FOLFOX6 (mFOLFOX6) ± 1 year of bevacizumab and failed to demonstrate significant benefits in 5-year DFS and OS between arms within stage II or III subgroups [28, 29]. Notably, the HR for recurrence within 15 months from start of study treatment was 0.61 (95% CI 0.48–0.78) in favor of bevacizumab, while a trend toward increased recurrence was noted after 15 months on the bevacizumab arm. A post hoc analysis of NSABP C-08 patients by mismatch repair status identified a potential survival benefit in the mismatch deficient cohort (HR 0.52, 95% CI 0.29–0.94) [30]. The AVANT phase III trial randomized 3451 patients with stage II or III disease to FOLFOX4 vs. FOLFOX4 + 1 year of bevacizumab vs. XELOX + 1 year of bevacizumab and failed to demonstrate significant improvement in DFS when bevacizumab was added to FOLFOX4 (HR 1.17, 95% CI 0.98–1.39, $p = 0.07$) or to XELOX (HR 1.07, 95% CI 0.90–1.28, $p = 0.44$), when compared to FOLFOX4 [31]. Like NSABP C-08, addition of bevacizumab was associated with improved DFS during initial study follow-up (DFS HR was 0.63 for FOLFOX4/bevacizumab and 0.61 for XELOX/bevacizumab compared to FOLFOX4 in the first year). However, this was offset by an overall trend toward increased recurrences in years 2 and 3 with addition of bevacizumab that translated into a trend toward a decrease in OS in the FOLFOX4/bevacizumab and XELOX/bevacizumab arms compared to FOLFOX4.

The QUASAR2 phase III trial randomized 1941 patients with stage II or III disease to receive 8 cycles of adjuvant capecitabine (24 weeks) ± bevacizumab every 3 weeks for 16 cycles (48 weeks) and similarly identified an improvement in DFS in the bevacizumab arm in the first 2 years, though this was offset by an increased recurrence rate after 2 years of follow-up leading to a DFS HR of 1.06 in the bevacizumab arm compared to control [32]. Subgroup analysis suggested a significant detrimental effect with bevacizumab in those with microsatellite stable tumors (HR 1.43, $p = 0.0005$), while no significant difference in outcomes was seen in those with microsatellite instable tumors (HR 0.74, $p = 0.42$). In conclusion, the addition of bevacizumab to conventional adjuvant chemotherapy has not provided a benefit in stage II or III colon cancer and may even be detrimental to DFS and OS in the long run. The favorable trends associated with bevacizumab in microsatellite instable tumors are hypothesis generating and warrant further investigation in this subgroup.

The role of adjuvant anti-epidermal growth factor (EGFR) agents in the adjuvant treatment of stage III colon cancer was investigated in two large phase III clinical trials. After subsequent protocol amendments, the N0147 phase III trial accrued 2070 patients with resected stage III *KRAS* wild-type (WT) tumors to be treated with adjuvant mFOLFOX6 ± cetuximab [33]. The addition of cetuximab did not demonstrate a benefit in 3-year DFS (HR 1.21, 95% CI 0.98–1.49) in those with *KRAS*-WT tumors or *KRAS/BRAF*-WT tumors when compared to mFOLFOX6. No survival benefits were also observed in any of the subgroup analyses. Notably, an exploratory analysis on previously closed arms in N0147 identified a nonsignificant trend toward improved DFS and OS with FOLFIRI/cetuximab compared to FOLFIRI [34]. The PETACC-8 phase III trial randomized patients with resected stage III disease to 6 months of FOLFOX4 ± cetuximab [35]. After subsequent amendment to include only those with *KRAS*-WT tumors similar to N0147, no significant improvement in DFS was identified with cetuximab in *KRAS*-WT (HR 1.05, 95% CI 0.85–1.29, $p = 0.66$) or *KRAS/BRAF*-WT (HR 0.99, 95% CI 0.76–1.28, $p = 0.92$) populations. On subgroup analysis, addition of cetuximab appeared to derive significant benefit in those with advanced T4 N2 tumors, while those with right colonic tumors and women experienced a significant DFS benefit with chemotherapy alone. Accordingly, results from N0147 and PETACC-8 have not identified a role for cetuximab in the adjuvant treatment of colon cancer. The potential benefit of cetuximab in T4 N2 disease is, at best, hypothesis generating. Although anti-EGFR therapy has shown increased tumor downstaging ability in metastatic disease, its disconnect in the adjuvant setting is unclear but may reside in the failure to induce complete pathologic sterilization.

Adjuvant Therapy in Elderly Patients with Stage III Colon Cancer

The median age at diagnosis for patients in the United States with stage III colon cancer is 72 years. Yet an early retrospective cohort study of 6262 patients aged ≥65 with resected stage III disease identified a steep decline in administration of adjuvant chemotherapy with increasing age at diagnosis ($p < 0.001$) as 78% of patients aged 65–69, 58% aged 75–79, and 11% aged 85–89 received postoperative chemotherapy [36]. Perceived barriers to the use of adjuvant chemotherapy in the elderly include coexisting morbidities, reluctance to receive chemotherapy, fear of increased toxicities, lack of social support, declining mental and functional status, and/or beliefs that potential benefits are negated by a short remaining natural life expectancy. Additionally, several major studies including the MOSAIC trial and NSABP C-07 failed

to show an unequivocal benefit from the addition of oxaliplatin to fluoropyrimidine chemotherapy in elderly patients.

An early pooled analysis of phase III trials involving postoperative 5-FU/LV or 5-FU/LEV vs. postoperative observation alone in stage II or III colon cancer patients grouped into four age categories (≤50, 51–60, 61–70, and >70) showed that adjuvant chemotherapy significantly improved DFS and OS (absolute 5-year survival advantage of 7%) compared to no adjuvant therapy regardless of how age was included in the analysis (p-values for test of interaction by age category were 0.61 for OS and 0.33 for DFS) [37]. Increased age was not significantly related to ≥ grade 3 AEs except for leukopenia in those receiving 5-FU/LEV ($p < 0.001$) and 5-FU/LV ($p = 0.05$, borderline significance). A recent pooled analysis on randomized control trials (RCTs) investigated adjuvant FOLFOX4 or XELOX vs. 5-FU/LV alone in stage III disease and, although modestly attenuated for patients aged ≥70, demonstrated superior DFS and OS with FOLFOX4/XELOX over 5-FU/LV regardless of age (DFS HR 0.77, 95% CI 0.62–0.95, $p = 0.014$ for age ≥ 70 group; OS HR 0.78, 95% CI 0.61–0.99, $p = 0.045$ for age ≥ 70 group) or medical comorbidities [38]. As expected, there were fewer grade 3–4 AEs in patients aged <70 with FOLFOX4/XELOX, though the rate of grade 3–4 neuropathy—the primary safety concern with oxaliplatin—was unrelated to increased age or medical comorbidity. Furthermore, a large cohort study of patients aged ≥67 with resected stage III colon cancer demonstrated that although patients with chronic conditions such as heart failure, chronic obstructive pulmonary disease (COPD), and diabetes were less likely to receive adjuvant chemotherapy than those without those conditions, the presence of such conditions did not consistently affect the ability to complete chemotherapy if initiated and the probability of all-cause, condition-specific, or toxicity-related hospitalizations associated with adjuvant chemotherapy [39]. In fact, patients with heart failure, COPD, or diabetes had higher 5-year survival rates when treated with adjuvant therapy for stage III disease than those untreated and with the same comorbidities.

It should be noted that increasing age will always be a poor prognostic factor for overall survival as the likelihood of dying from noncancer causes increases as one ages [40]. Nevertheless, analyses have identified that elderly patients, like their younger counterparts, can derive significant survival benefits with adjuvant chemotherapy in stage III colon cancer without significant increases in toxicity and irrespective of medical comorbidity.

Adjuvant Chemotherapy in Stage II Colon Cancer

Approximately 25% of all cases of colon cancer are accounted by stage II disease [4]. Of all patients with colon cancer, about 20% have stage IIA disease, 2% have stage IIB disease, and 2% have stage IIC disease. Stage II colon cancer carries a 5-year DSS rate of 84.7% and 5-year OS rate of 70.3% [5]. The 5-year DSS rates for stage IIA, IIB, and IIC disease are roughly 85%, 79.4%, and 64.9%, respectively, while 5-year OS rates for stage IIA, IIB, and IIC disease are about 70%, 63.2%, and 54.6%, respectively. Unlike stage III colon cancer, for which postoperative treatment is universally recommended, the benefit of adjuvant chemotherapy in stage II disease remains under debate.

A retrospective subgroup analysis of 318 patients with resected stage II disease originally enrolled in INT-0035 demonstrated that 5-FU/LEV reduced the recurrence rate by 31% at 7 years compared to postoperative observation alone, though this trend was not significant (relative risk [RR] 0.69, 95% CI 0.44–1.08, $p = 0.10$) [41]. OS at 7 years was nearly identical in both arms (72% in 5-FU/LEV vs. 72% postoperative observation, $p = 0.83$); such disparities have been attributed to an underpowered study, a high noncancer death rate, and higher rates of salvage surgery on the observation arm. Notably, this analysis suggested that patients with prognostic features associated with increased recurrence rates—such as adhesion or invasion of adjacent organs, obstruction, perforation, or location of primary tumor (of which only the latter three reached significance $p < 0.05$)—may benefit from adjuvant chemotherapy.

A meta-analysis of NSABP protocols C-01, C-02, C-03, and C-04 explored the benefits of adjuvant chemotherapy in 1565 patients with resected stage II colon cancer by combining treatment arms from all four trials with inferior OS, DFS, and RFS (surgery alone in C-01 and C-02, MOF in C-03, and 5-FU/LEV in C-04) into treatment 1 vs. combining treatment arms with superior survival (MOF in C-01, perioperative portal vein infusion of 5-FU in C-02, 5-FU/LV in C-03 and C-04) into treatment 2 [42]. At 5-year follow-up, the cumulative odds of mortality were 0.70 in patients with stage II disease in treatment 2 (30% mortality reduction over treatment 1 for stage II disease). Adjuvant chemotherapy conferred an absolute survival benefit of 5% in stage II disease regardless of prognostic factors for recurrence (5-year OS of 87% treatment 2 vs. 82% treatment 1 with low-risk characteristics, 75% treatment 2 vs. 70% treatment 1 with high-risk characteristics Table 7.4) [42–44].

In 1997, the International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators performed a meta-analysis of RCTs comparing adjuvant 5-FU/LV to surgery alone in 1025 patients with stage II colon cancer [43]. At 5 years, event-free survival (EFS) and OS were not significantly improved with adjuvant 5-FU/LV compared to postoperative observation alone (Table 7.4). Nonetheless, enrollment began in 1994 for the Quick And Simple And Reliable (QUASAR) phase III trial investigating 5-FU (370 mg/m^2 IV) + low-dose LV (25 mg IV) or high-dose LV

Table 7.4 Adjuvant therapy in stage II colon cancer

Study	*n* = size	Arms	DFS[a]	OS[a]
NSABP C-01, C-02, C-03, C-04 meta-analysis [42]	1565	Treatment 2 vs. treatment 1	Reductions in DFS and RFS regardless of stage; reductions were as great or greater for stage II patients as for stage III patients[b]	30% mortality reduction over treatment 1[b]; OS of 87% treatment 2 vs. 82% treatment 1 in low-risk patients, 75% treatment 2 vs. 70% treatment 1 in high-risk patients[c]
IMPACT B2 [43]	1025	5-FU/LV vs. observation	EFS 0.76 vs. 0.73 (HR 0.83, 95% CI 0.68–1.01, $p = 0.061$)	0.82 vs. 0.80 (HR 0.81, 95% CI 0.64–1.01, $p = 0.057$)
QUASAR [44]	3239	5-FU/LV ± LEV (allowed until 1997) vs. observation	RR 0.78 (95% CI 0.67–0.91, $p = 0.001$)	RR 0.82 (95% CI 0.70–0.95, $p = 0.008$) Absolute improvement in OS of 3.6% (95% CI 1.0–6.0)

DFS disease-free survival, *OS* overall survival, *Treatment 1* combination of surgery alone arm from C-01 and C-02, MOF arm from C-03, and 5-FU/LEV arm from C-04, *Treatment 2* combination of MOF arm from C-01, perioperative portal vein infusion of 5-FU arm from C-02, and 5-FU/LV arm from C-03 and C-04, *RFS* relapse-free survival, *5-FU* 5-fluorouracil, *LV* leucovorin, *EFS* event-free survival, *HR* hazard ratio, *CI* confidence interval, *LEV* levamisole, *RR* relative risk

[a]5-year unless otherwise specified

[b]*p*-values not reported

[c]High risk defined as the presence of obstruction, bowel perforation, or extension of tumor into adjacent organs

(175 mg IV) ± levamisole (until 1997, 12 courses of 450 mg over 3 days repeated every 2 weeks) given as six 5-day courses every 4 weeks or 30 once-weekly courses vs. observation in 3239 patients primarily with stage II colorectal cancer having undergone resection in the prior 6 weeks [44]. Adjuvant 5-FU/LV improved 5-year OS and DFS compared to postoperative observation alone, and assuming 5-year mortality without chemotherapy was 20%, the benefits seen with adjuvant chemotherapy translate into an absolute improvement in OS of 3.6% (95% CI 1.0–6.0) in a study population consisting predominantly of stage II colon cancer.

Subgroup analysis on the 10-year follow-up to the MOSAIC study demonstrated that adjuvant FOLFOX4 afforded a nonsignificant absolute improvement in OS of 3.7% over LV5FU2 (75.4% vs. 71.7%, $p = 0$ 0.058) in patients with high-risk stage II colon cancer (defined as presence of T4 disease, tumor perforation, or <10 lymph nodes examined) [21]. Notably, adjuvant FOLFOX4 was detrimental to 10-year OS in those with low-risk stage II disease compared to LV5FU2 (81.2% vs. 86.7%). Similar nonsignificant improvement was seen in 10-year DFS (absolute improvement of 5.7%) in those with high-risk stage II disease treated with adjuvant FOLFOX4 compared to LV5FU2, while a nonsignificant detrimental effect was seen in DFS (absolute decrement of 2.3%) in those with low-risk stage II disease treated with adjuvant FOLFOX4 compared to LV5FU2.

To summarize, at the time of the convening of an American Society of Clinical Oncology (ASCO) panel in 2003, it was recognized that about 25% of patients with resected stage II colon cancer will develop recurrence within 5 years [45]. Accordingly, adjuvant therapy (capecitabine, 5-FU/LV, or FOLFOX) could be considered and justified in stage II disease with high-risk features for recurrence (<12 lymph nodes sampled; bowel obstruction; perforation at tumor site; poorly differentiated histology [exclusive of MSI-H tumors]; perineural invasion; lymphovascular invasion; or close, indeterminate, or positive margins)—though this decision is not mandated by National Comprehensive Cancer Network (NCCN) guidelines [46]. Similarly, adjuvant capecitabine or 5-FU/LV (but not FOLFOX, FLOX, or XELOX) remains an option in patients with stage IIA and MSI-L/MSS tumors without high-risk characteristics—though, again, this is not mandated by NCCN guidelines. Importantly, the decision to undergo adjuvant chemotherapy in stage II disease must include a discussion between patient and oncologist regarding the risks, benefits, and alternatives with an understanding that the magnitude of improvement is small (no more than 5% absolute improvement in 5-year survival).

Prognostic and Predictive Biomarkers and Adjuvant Therapy in Stage II and III Colon Cancer

Microsatellite Instability

Initially described by researchers in the early 1990s, microsatellite instability (MSI) represents an abnormal shortening or lengthening of ubiquitous deoxyribonucleic acid (DNA) segment repeats (microsatellites) caused by defective DNA mismatch repair (MMR) and is found in approximately 15% of cases of colorectal cancer [47]. The National Cancer Institute (NCI)-sponsored international workshop in 1997 originally defined MSI as graded high (MSI-H) when instability was present in ≥2 markers, graded low (MSI-L) when instability was present in one marker, and graded stable (MSS) when all markers were stable from a reference panel of markers [47]. MSI-L and MSS tumors are often grouped together as they appear to be phenotypically similar, while MSI-H tumors have been associated with improved survival in nonmetastatic colorectal cancer.

A retrospective, multicenter study involving 303 patients with stage III colon cancer was among the first to demonstrate that patients with MSI-H or defective MMR (dMMR) tumors experienced improved DFS at 3 years (90.5%) compared to those with MSI-L/MSS or proficient MMR (pMMR) tumors (73.8%, 95% CI 67.9%–78.8%, $p = 0.027$) when treated with adjuvant FOLFOX (FOLFOX4 or mFOLFOX6) [48]. Significantly less relapses at 3-year follow-up were also identified in patients with MSI-H tumors (10.5%, defined as ≥3 unstable markers) vs. those with MSS tumors (35.0%, $p = 0.04$, defined as <3 unstable markers) treated with adjuvant FOLFOX4 for stage II or III disease in a prospective but small study [49]. An analysis of stage II or III colon cancer patients from NSABP C-07 and C-08 showed that adjuvant oxaliplatin-based therapy (FLOX or mFOLFOX6) improved 3-year time-to-recurrence in dMMR tumors (87.6%) vs. pMMR tumors (78.0%, HR 0.58, 95% CI 0.35–0.96, $p = 0.03$)—though this analysis was limited by very low numbers of recurrences and dMMR tumors [50].

In the updated 10-year follow-up of the MOSAIC study, adjuvant FOLFOX4 demonstrated a trend in favor of improved DFS (HR 0.48, 95% CI 0.21–1.12, $p = 0.88$) and OS (HR 0.41, 95% CI 0.16–1.07, $p = 0.69$) vs. LV5FU2 in dMMR tumors though significance was not reached due to the low incidence of dMMR tumors and low statistical power [21]. Recently, a retrospective, multicenter study of 433 patients with stage II or III disease with MSI showed that 3-year relapse-free survival was significantly improved with adjuvant FOLFOX (HR 0.46, 95% CI 0.23–0.79) but not with adjuvant 5-FU (HR 1.02, 95% CI 0.60–1.73); on subgroup analysis, the benefit of adjuvant FOLFOX was significant in stage III colon cancer with a trend toward significance in stage II disease [51].

In a pooled analysis of RCTs involving adjuvant 5-FU chemotherapy in stage II or III colon cancer, patients with dMMR tumors treated with adjuvant 5-FU gained no benefit in DFS compared to postoperative observation alone [52]. Patients with stage II disease and dMMR tumors treated with adjuvant 5-FU experienced reduced OS (HR 2.95, 95% CI 1.02–8.54, $p = 0.04$) vs. surgery alone. Some have proposed that given the favorable prognosis and evidence of lack of benefit from adjuvant 5-FU in stage II colon cancer with dMMR, these patients should not receive adjuvant 5-FU chemotherapy. In stage III colon cancer with dMMR, there is growing evidence to support a potential advantage with adjuvant FOLFOX over 5-FU, though this remains to be definitively defined in a large, randomized control setting. In summary, evidence is mounting for the role of MSI as a prognostic and predictive biomarker in the adjuvant treatment of colon cancer. Patients with low-risk stage II MSI-H tumors should be followed with observation, while adjuvant FOLFOX is a consideration in those with high-risk stage II disease and MSI-H tumors. Patients with MSI-H stage III disease should be strongly considered for oxaliplatin plus fluoropyrimidine adjuvant therapy. MSI should be tested anytime fluoropyrimidine monotherapy is considered.

Gene Signatures in Stage II Colon Cancer

The Oncotype DX® colon cancer assay was developed using a gene expression profile from patients with stages II and III colon cancer enrolled in NSABP trials and an observational cohort from the Cleveland Clinic to generate a recurrence score (RS) (scaled from 0 to 100) from a final set of 12 genes in an effort to better delineate risk of recurrence and guide adjuvant therapy decision making [53]. The 12-gene RS was initially validated in 1436 patients with stage II disease from the QUASAR study, which showed that risk of recurrence was significantly associated with RS (HR per interquartile range 1.38, 95% CI 1.11–1.74, $p = 0.004$) with recurrence risks at 3 years of 12%, 18%, and 22% for low, intermediate, and high RS groups of <30, 30–40, and ≥41, respectively [54]. After adjusting for other clinicopathologic parameters, the RS, T stage, and MMR status were the most significant independent predictors of recurrence after surgery. Moreover, as relative benefit of adjuvant 5-FU/LV was independent of the RS, patients with a higher RS were expected to derive more absolute benefits from adjuvant 5-FU/LV. These findings were confirmed in a CALGB validation study that also showed that the 12-gene assay was useful in a majority of patients with stage II disease for which T stage and MMR status are not informative, as it was able to identify 22% of patients having T3 disease (stage IIA) and pMMR tumors with a high RS that estimates an average 5-year recurrence risk of 21% [55]. Furthermore, a NSABP validation study showed that the absolute benefit from addition of oxaliplatin to adjuvant therapy in stage II disease increased with higher RS [56].

A prospective, multicenter study analyzed the influence of the 12-gene assay on clinical decision making in patients with stage IIA disease (T3 disease and pMMR tumors) in the adjuvant setting. For each patient, the adjuvant treatment plan of observation, fluoropyrimidine monotherapy, or combination therapy with oxaliplatin recommend by the physician was recorded before and after the RS results were provided. It was noted that treatment recommendations changed in 45% of patients and intensity of treatment (monotherapy vs. combination therapy) decreased for 33% of patients after RS results were provided to the physician [57]. Increased treatment intensity was seen with a higher RS and decreased intensity seen with a lower RS ($p = 0.011$).

Additionally, *ColoPrint*® is an 18-gene colon cancer assay validated in 206 patients with stage I–III disease [58]. This signature designated 63.2% of patients at low risk of recurrence (5-year RFS 87.6%) and 36.8% at high risk (5-year RFS 67.2%). Notably, among 67 patients classified as MSI-H, only 53 were classified as low-risk. Therefore,

ColoPrint® may not only be able to detect low-risk patients with stage II disease but also be able to identify low-risk patients *beyond* MSI-H status who may be able to forgo adjuvant chemotherapy. *Colorectal Cancer DSA (ColDx)*® is a recent 634 gene transcript microarray signature that identified patients at higher risk of recurrence for stage II colon cancer in an independent validation employing 73 patients with recurrent disease (high risk) and 142 patients with no recurrence (low risk) within 5 years of surgery [58]. This signature is currently undergoing prospective validation and is not available outside the context of a clinical trial.

In short, as the role of adjuvant therapy in stage II disease remains under debate, various gene expression signatures under development may serve as additional tools for individualized recurrence risk assessment, exploring decisions, risks, and benefits to initiating adjuvant chemotherapy (particularly in stage IIA and pMMR tumors), and guiding decisions on intensity (FOLFOX vs. 5-FU monotherapy) of adjuvant therapy.

Adjuvant and Neoadjuvant Therapy for Rectal Cancer

Background and Staging

Approximately 40,000 patients are diagnosed with rectal cancer annually in the United States [59]; 70–80% of cases are diagnosed in the localized or locally advanced setting, wherein treatment is usually multidisciplinary, involving surgery and often chemotherapy and/or radiotherapy. The rectum is contiguous with the colon and the anus. Its upper portion reaches the peritoneal reflection, being covered anteriorly and laterally by peritoneum, though the vast majority of the rectum is entirely extraperitoneal. From a surgical standpoint, the anal verge (distal end of the anal canal) and the dentate line (transition between squamous and columnar mucosa) represent the other major landmarks. The dentate line serves as the inferior margin of the rectum. The precise upper limits of the rectum have been the subject of debate, ranging from 10 to 15 cm from the anal verge, with variable clinical trial and clinical practice definitions. The NCI Guidelines 2000 for Colon and Rectal Cancer Surgery established that lesions with an inferior margin greater than 12 cm from the anal verge by rigid proctoscopy should be considered as sigmoid colon rather than rectum [60]. This is clinically and anatomically relevant, as historic retrospective data have suggested that whatever the nomenclature, tumors greater than 12 cm have local recurrence rates more similar to that of colon cancer: 10% rather than 30% [61]. Modern surgical data for patients undergoing the current gold standard surgery, transmesorectal excision (TME), have continued to demonstrate that higher rectal tumors are at lesser risk for local recurrence [62]. In planning therapy, the exact location of the tumor is most reproducibly assessed through endoscopic examination via rigid proctoscopy, making this the most useful tool for precisely defining upper rectal tumors. Colonoscopy is useful as part of the initial work-up in evaluation for synchronous lesions, but it should not necessarily replace rigid proctoscopy by the involved surgeon. This is a key component of staging and can alter the treatment plan or included modalities in a substantial portion of patients [63].

In addition to endoscopy, optimal pretherapy staging of rectal cancer involves both systemic and local tumor (T) and nodal (N) staging. Most typically, a computed tomography (CT) scan of the chest, abdomen, and pelvis with intravenous contrast is utilized to assess for metastatic disease. However, CT imaging alone does not accurately assess the depth of tumor mural invasion or nodal involvement. Thus, pelvic magnetic resonance imaging (MRI) or rectal endoscopic ultrasound (EUS) is a must for accurate determination of staging and appropriate treatment. Either test is acceptable. Ultrasound is a more operator-dependent modality, but it may provide slightly improved accuracy in the T staging of early rectal cancers [64]. A significant advantage of MRI, on the other hand, is that it allows for assessment of the circumferential resection margin (CRM). The CRM is of significant import in the treatment of locally advanced rectal cancers, critical for successful local tumor control [65].

Historically, rectal cancer has been plagued by unacceptably high rates of postoperative local recurrence, upward of 30% [61]. This is thought to be largely related to subpar removal of the full associated perirectal nodal basin and inconsistent achievement of a clear radial surgical margin. A positive circumferential resection margin represents the major risk factor for local recurrence, linked also to poorer rates of distant metastases and long-term survival [66]. With the recognition that the integrity of the mesorectum and the associated mesorectal fascia need be preserved, surgical techniques improved. The advent of TME—wherein resection involves removal of both the rectum and mesorectum via an approach along the mesorectal fascial plane—brought single-institution reports of local failure rates to as low as 4–9% [67]. In the multinational TME study, a 5-year local recurrence rate of 10.9% was achieved with the TME surgical technique alone [62, 68]. Still, in very-low-lying rectal tumors, the narrowing of the mesorectum, the lack of a significant mesorectal fat plane as the anal levators are approximated, and a narrow pelvis, which can hamper access, collectively constrain optimal surgical outcome. Likely related to these factors, abdominoperineal resection (APR), the surgery required for low rectal tumors, is linked to increased rates of a positive CRM, increased rates of local recurrence, and decreased rates of cancer-specific survival [69].

Currently, as stage I rectal cancers have low rates of recurrence post resection, the standard treatment for early rectal

cancers consists of surgery alone. The risk of regional lymph node involvement is low; accordingly, both local and distant recurrences are uncommon. Stage II and III rectal cancers are collectively referred to as locally advanced. Due to the elevated risk of both local and systemic recurrence, the current standard of care in locally advanced disease consists of neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy.

It is important to recognize that not all locally advanced rectal cancers carry the same risk of local and/or distant recurrence. In addition to CRM involvement and a low-lying position, a T4 tumor, advanced nodal stage, the extent of extramural tumor spread, and extramural venous invasion are additional risk factors for recurrence. Commonly encountered T3 tumors can vary widely in appearance and risk, from those that invade the mesorectal fascia to those that barely pass through the muscularis propria. Tumors with limited extramural extension (≤5 mm) fare much better than those with extensive spread (>5 mm). Local recurrence rates stand at 10.4% and 26.3%, with 5-year survival of 83.4% vs. 54.1%, respectively, for limited and extensive spread [70]. These differences in outcome based on extramural extension persist even when assessed pathologically postneoadjuvant chemoradiation [71]. MRI can also be utilized to assess extramural venous invasion, similarly linked to both local and distant recurrence [72, 73]. While current treatment standards endorse the full gamut of therapies, certain patients are encumbered with the toxicity, but likely derive minimal absolute benefit. Patients with high-risk factors are presumably the ones who have opportunity to derive maximal benefit from multimodality therapy. T3 N0 tumors that lack additional features of risk may not benefit substantially from the full spectrum of perioperative therapies, provided high-quality staging and surgery are undertaken.

Adjuvant Radiotherapy and Chemoradiation

Prior to the evolution of surgical technique, radiotherapy was introduced to the rectal cancer treatment paradigm as a means to combat the local recurrence rates of >30%. Initial efforts utilized adjuvant radiotherapy with antiquated techniques and suboptimal radiosensitizing chemotherapy regimens. Two major studies compared radiation-based strategies or chemotherapy to observation alone. GITSG protocol 7175 randomized 227 patients with resected Dukes B2 or C rectal cancer to one of the four arms: observation, chemotherapy (5-FU and semustine), radiotherapy, or combined chemoradiotherapy with 5-FU followed by maintenance chemotherapy (5-FU and semustine). Compared to observation alone, chemoradiation reduced the risk of recurrence from 55% to 33% and in a latter report improved overall survival [74, 75].

NSABP R-01 randomized 555 patients with resected Dukes B and C rectal cancer to observation, radiotherapy, or chemotherapy with MOF (5-FU, semustine, and vincristine). At 5 years, radiation reduced locoregional recurrences as compared to observation alone, but no difference in disease-free or overall survival was witnessed. On the other hand, adjuvant MOF conferred a disease-free and overall survival advantage compared to observation alone [76].

The NCCTG 794751 study randomized 204 patients with resected Dukes B2 or C rectal cancer to adjuvant radiotherapy vs. chemoradiation (with 5-FU). In the chemoradiation arm, adjuvant chemoradiation (with bolus 5-FU) was preceded by 1 cycle and followed by 2 cycles of chemotherapy (5-FU and semustine). At a median follow-up of over 7 years, the risk of local recurrence was decreased by 46% and distant metastases were reduced by 37%. In addition, there were improvements in cancer-specific and overall survival, with the death rate decreased by 29% [77].

These initial studies set chemoradiation as a standard component of therapy for locally advanced rectal cancer, with differences in survival seen with some but not all approaches—albeit in the setting of substandard chemotherapy, radiotherapy, and surgery. Subsequent studies have served to optimize the timing of therapy and optimal chemosensitizing agents. These have not led to consistent improvements in DFS or OS; however, there is little doubt that improvements in toxicity profile and local control rates have been achieved.

Neoadjuvant Versus Adjuvant Chemoradiation

The German rectal cancer study evaluated the role of preoperative versus postoperative chemoradiation in a trial of 823 patients with T3, T4, or node-positive rectal cancers. Infusional 5-FU (1000 mg/m^2/day, on days 1–5 and 29–33) was administered concomitantly with 50.4 Gy of radiation administered in 28 fractions. TME was performed for all patients. There was no difference seen in disease-free or overall survival. However, through preoperative chemoradiation, pathologic downstaging was evident, with an 8% rate of pathologic complete response, and higher rates of sphincter-preserving surgery achieved: 39% vs. 19%. This translated into a significant reduction in the risk of local relapse at 5 years (6% vs. 13%) [78]. At 10 years, the benefit lessened (7.1% vs. 10%), but remained significant [79]. Additionally, both acute and long-term rates of severe toxicity were reduced with preoperative therapy as compared to postoperative therapy. Given the improvements in local recurrence rates and lesser toxicity, the preoperative setting has gained traction as the standard approach for administration of chemoradiation.

Given that chemoradiation has consistently reduced the rates of local recurrence, but has a less clear role on survival, some studies have looked to eliminate this modality. The

MRC CR07/NCIC-CTG C016 study randomized 1350 patients with resectable rectal cancer to preoperative short-course radiation versus selective postoperative chemoradiation for those patients with a + CRM. Patients of stages I–III were included. Preoperative radiotherapy resulted in an absolute difference in the local recurrence rate of 6.2%: 10.6 vs. 4.4%. A relative improvement in disease-free survival of 24% was additionally noted, translating into a 6% median absolute difference (77.5% vs. 71.5%). Survival was no different. It must be pointed out that there are substantial limitations to this study. A distinct minority of the selective radiotherapy population (<10%) received radiotherapy due to a + CRM [80]. Though a majority of surgeries were intended as true TME, evidence suggests inadequate surgical technique in nearly 50% of cases [81]. This is an important risk factor for local recurrence. On further examination, those patients who had optimal surgical resection in the mesorectal plane had the lowest rates of local recurrence; those who also received preoperative therapy had a local recurrence rate of only 1%. On the one hand, this study raises concern for the selective use of postoperative chemoradiotherapy. On the other hand, this study is clearly flawed. It highlights vital complicating factors in the interpretation of these multimodality studies, as well as issues in comparing study results over time, as techniques evolve. Standardization to achieve optimal surgical technique as well as optimal preoperative imaging to assess for an at-risk mesorectal fascia plane has given very different results.

Neoadjuvant Chemoradiation

Chemoradiation with Fluoropyrimidines

Two large trials served to cement the place for preoperative chemoradiation. FFCD 9203 and EORTC 22921 compared preoperative chemoradiation with 5-FU to radiotherapy alone. FFCD 9203 randomized 733 patients with T3 or T4 rectal cancer to a course of RT (45 Gy over 25 fractions), with or without bolus 5-FU and leucovorin (LV) (days 1–5 and 29–33). Both arms received adjuvant 5-FU. With this approach, 5-year survival did not differ, but local recurrence decreased from 16.5% to 8.1%. A pathologic CR (pCR) rate of 14.6% was achieved [82]. EORTC 22921 randomized 1011 patients to the same doses of chemotherapy and radiotherapy in a 2 × 2 fashion: preoperative radiotherapy alone versus preoperative chemoradiation plus or minus adjuvant chemotherapy (5-FU 350 mg/m^2/day × 5 days + LV 20 mg/m^2/day × 5 days, every 28 days) [83]. The pCR rate was improved with chemoradiation (5.3% vs. 13.7%) [84]. In the three arms that received chemotherapy at any juncture, local recurrence was also improved as compared to the radiotherapy-only arm [83]. At a median of greater than 10 years long-term follow-up, no difference in disease-free or overall survival emerged between the arms [85].

The optimal chemotherapy regimen to be given with radiotherapy has been extensively evaluated. Key studies are depicted in Table 7.5 [79, 80, 82, 85–88]. Two large randomized trials pitted adjuvant radiation with bolus 5-FU versus infusional 5-FU, based on preclinical data suggesting improved radiosensitization with prolonged 5-FU exposure. The NCCTG compared infusional 5-FU (225 mg/m^2/day continuously through radiotherapy) with bolus 5-FU (500 mg/m^2 days 1–3 and 29–31) in patients with stage II or III rectal cancer. Adjuvant chemotherapy (bolus 5-FU and semustine) was administered in a "sandwich" fashion prior to and after chemoradiation in both arms. Though local recurrence did not differ, both disease-free (53% vs. 63%) and overall survival (60% vs. 70%) were improved in the continuous infusional 5-FU arm [86]. Grade 3/4 diarrhea was more common with infusional 5-FU therapy: 24% vs. 14%. A second larger intergroup study, INT 0144, evaluated stage II and III rectal cancer, comparing the merits of delivering 5-FU as a continuous infusion versus in a bolus fashion with radiation and as adjuvant therapy. Two arms utilized continuous infusional 5-FU (225 mg/m^2/day) concomitantly during radiotherapy, while a third utilized bolus 5-FU (400 mg/m^2 days 1–4 and 29–32) plus leucovorin. Adjuvant therapy comprised either bolus or infusional 5-FU. Contrary to the NCCTG study, at greater than 5-year median follow-up, disease-free and overall survival were no different between the arms. However, grade 3/4 hematologic toxicity was substantially less with infusional therapy: 4% vs. 49–55% [87].

The oral fluoropyrimidine, capecitabine, has been studied as an alternative to 5-FU for radiosensitization. The lack of need for a central venous catheter is appealing, though variable metabolism and increased reliance on a compliant patient are potential concerns. A German phase III study randomized 401 patients with clinical or pathologic stage II and III rectal cancer to undergo neoadjuvant or adjuvant chemoradiation with capecitabine (1650 mg/m^2/day daily) or infusional 5-FU (1000 mg/m^2/day, days 1–5, 29–33) with additional adjuvant chemotherapy. At a median follow-up of 52 months, 5-year overall survival was noninferior with use of capecitabine. Additionally, no difference was seen in disease-free survival or local recurrence rates [89]. NSABP R-04 examined neoadjuvant chemoradiation through randomization of 1608 patients with stage II and III rectal cancer in a 2 × 2 fashion: infusional 5-FU or capecitabine with or without oxaliplatin. The 3-year local recurrence rates, 5-year DFS, and 5-year OS were unchanged between the 5-FU and capecitabine arms. Toxicity was similar between the two arms. Due to a safety signal of severe diarrhea, an amendment was put though prior to 20% of enrollment that decreased treatment from 7 to 5 days per week (Monday to Friday). With this change, rates of grade 3 or greater diarrhea decreased from 15% to 17% to 6.9% with both 5-FU and capecitabine [88].

Table 7.5 Select trials of neoadjuvant and adjuvant chemoradiation with fluoropyrimidines

Trial	No. of patients	Radiotherapy regimen	Adjuvant chemo	pCR rate	Local recurrence	5-year disease-free survival	5-year overall survival	Grade III/IV adverse event rates	
FFCD-9203 [82]	733	45 Gy/25 Fx with 5-FU vs. 45 Gy/25 Fx	Bolus 5-FU	11.4% 3.6% ($p < 0.0001$)	8.1% 16.5% ($p = 0.004$)	59.4% 55.5% (ns)	67.4% 67.9% ($p = 0.684$)	14.6% 2.7%	
EORTC 22921 [85]	1011	45 Gy/25 Fx with bolus 5-FU vs. 45 Gy/25 Fx	Randomized in a 2 × 2 fashion to bolus 5-FU or observation	13.7% 5.3% ($p < 0.001$)	8.7% 17.1% ($p = 0.002$)	NR	65.8% 64.8% ($p = 0.84$)	13.9% 7.4%	
CAO/ARO/AIO-94 [79]	823	50 Gy/28 Fx Preoperative vs. Postoperative	Both arms: Bolus 5-FU	8% N/A	6% 13% ($p = 0.006$)	NR	76% 74% ($p = 0.8$)	27% 40%	
NCCTG [86] O'Connell et al. (postoperative)	680	50+ Gy/25+ Fx + bolus 5-FU vs. 50+ Gy/25+ Fx + CIVI 5-FU	Both regimens randomized: bolus 5-FU +/− semustine	N/A	NR	(4-year) 53% 63% ($p = 0.01$)	(4-year) 60% 70% ($p = 0.005$)	Severe diarrhea: 14% vs. 24% Severe leukopenia: 11% vs. 2%	
								GI	Heme
INT 0144 [87] (postoperative)	1917	50 Gy/28 Fx + CIVI 5-FU vs. 50 Gy/28 Fx + CIVI 5-FU vs. 50 Gy/28 Fx + bolus 5-FU	Bolus 5-FU Infusional 5-FU Bolus 5-FU + LV	N/A	8% 4.6% 7%	62% 62% 57% ($p = 0.25$)	68% 71% 68% ($p = 0.5$)	41% 42% 44%	55% 4% 49%
German Trial [80] *Hofheinz* et al. (preoperative OR postoperative)	401	50 Gy/28 Fx + Capecitabine vs. 50 Gy/28 Fx + bolus 5-FU	Capecitabine Bolus 5-FU	14% (of 73) 5% (of 74) ($p = 0.09$)	6% 7% ($p = 0.67$)	68% 54%	76% 67% ($p = 0.05$)	Grade 3/4 diarrhea: 17% vs. 4% Grade 3/4 leukopenia: 3% vs. 16%	
NSABP R-04 [88]	1608	50 Gy/28 Fx + capecitabine vs. 50 Gy/28 Fx + CIVI 5-FU	N/A	20.7% 17.8% ($p = 0.14$)	11.8% 11.2% ($p = 0.98$)	67.7% 66.4% ($p = 0.7$)	80.8% 79.9% ($p = 0.38$)	No difference	

5-FU fluorouracil, *Cape* capecitabine, *CapeOx* capecitabine + oxaliplatin, *CIVI* continuous intravenous infusion, *FOLFOX* folinic acid + 5-FU + oxaliplatin, *Fx* fraction, *Gy* gray, *N/A* not applicable, *NR* not reported, *NS* not significant

Chemoradiation with Additional Agents

Although oxaliplatin has a clear role in metastatic colorectal cancer as well as the adjuvant therapy of colon cancer, its role as a radiosensitizing agent is unclear. Multiple studies have examined this to date including STAR-01, ACCORD 12/0405 PRODIGE 2, PETACC-6, NSABP R-04, CAO/ARO/AIO-04, and the FOWARC trial (Table 7.6) [88, 90–93]. As compared to radiotherapy with a fluoropyrimidine alone, oxaliplatin increased toxicity in all studies. In NSABP R-01, rates of grade 3/4 toxicities were significantly greater with oxaliplatin, namely, diarrhea, neuropathy, and fatigue [88]. Two of the studies have shown an increase in pCR rate with oxaliplatin, CAO/ARO/AIO-04 (17% vs. 13%) and FOWARC (31% vs. 13%), but the other four have demonstrated no such difference [94]. To date, long-term outcomes are reported in four studies. Three of these, NSABP-R04, ACCORD 12/0405 PRODIGE 2, and PETACC-6, have demonstrated no differences in local control, disease-free survival, or overall survival [76, 88, 95]. On the other hand, at a median 50-month follow-up, the study that would seem to be the outlier, CAO/ARO/AIO-04, demonstrated improved 3-year disease-free survival (75.9% vs. 71.2%) and a similar incidence of late toxicities. The increased rate of severe acute toxicity and lack of a consistent benefit have dampened enthusiasm for the inclusion of oxaliplatin. At this point, oxaliplatin should not be considered as a standard component of chemoradiation.

Additional agents have been explored in combination with radiotherapy, including irinotecan, bevacizumab, cetuximab, and panitumumab. None has demonstrated conclusive evidence of benefit. Bevacizumab may increase response rates, including complete response rates, though comparative data are limited and data on long-term outcomes are immature [96–98]. Enthusiasm for adding bevacizumab to perioperative therapy is countered by the negative adjuvant colon cancer studies, a lack of data showing consistently improved response rates, and the potential for heightened rates of postoperative complications [99]. EGFR inhibition with cetuximab was studied in the EXPERT-C study, wherein patients with high-risk rectal cancer received preoperative and postoperative CAPOX (capecitabine + oxaliplatin) and capecitabine-based chemoradiation, with or without cetuximab. High risk was defined as one of the following on MRI: T3 tumor at or below the levators, T4, tumor within 1 mm of CRM, >5 mm extramural extension, or presence of extramural venous invasion. As data on RAS and EGFR resistance emerged, this study was amended for analysis of the primary endpoint, complete response rate, in KRAS and BRAF WT patients. In a RAS WT population, at >5-year median follow-up, the cetuximab arm demonstrated numerically higher but not statistically different rates of complete response (15.8% vs. 7.5%), 5-year progression-free survival (75.5% vs. 67.5%), and 5-year overall survival (83.8% vs. 70%) [100]. Further definitive studies are lacking. This would seem worthy of further study, but at present remains investigational only.

In sum, when considering radiosensitizers for neoadjuvant therapy, there are multiple options. Key studies suggest slightly differing toxicity profiles for the bolus 5-FU and infusional 5-FU regimens, with a hint of possible differences in efficacy. While either regimen can be justified, in general, infusional 5-FU has been favored as the optimal radiosensitizing agent. In addition, randomized data fully support capecitabine as a viable alternative for utilization with radiation. At this point, there is no role for additional chemotherapeutics or targeted agents with radiation outside of a clinical trial.

Neoadjuvant Short-Course Versus Long-Course Radiation

While long-course chemoradiation has been embraced in the United States and other parts of the world, in some countries, preoperative short-course radiation (5 Gy × 5 fractions) has become the standard. The MRC CR07/NCIC-CTG C016 study comparing short-course preoperative radiation to selective postoperative chemoradiation was previously described. This study demonstrated disease-free survival and local recurrence benefits, though with limitations related to suboptimal surgical technique. Two additional major studies examined short-course radiation vs. surgery alone: the Swedish Rectal Cancer Study and the Dutch Colorectal Cancer Group (DCCG) TME Study. In the Swedish study of 1168 patients, results at a median follow-up of 13 years revealed improvements in local recurrence (9% vs. 26%), cancer-specific survival (72% vs. 62%), and overall survival (38% vs. 30%) with radiation compared to surgery alone. There was no difference in the rates of distant metastases [101]. The Dutch study randomized 1861 patients undergoing TME to short-course radiotherapy or observation. In long-term follow-up, the 10-year rate of local recurrence with preoperative radiotherapy was half that seen with surgery alone (5% vs. 11%). Overall survival was no different in the overall population. In an exploratory subgroup analysis, there was suggestion of potential benefit in the stage III population [102].

Naturally, preoperative long-course chemoradiation and short-course radiotherapy have been compared head-to-head in at least two medium-sized studies (Table 7.7 [73, 80, 102, 103, 104]). A Polish study utilizing bolus 5-FU and LV on days 1–5 and 29–33 enrolled 316 patients with T3 and T4 rectal cancer. At 4 years, there was no difference in DFS (58.4% vs. 55.6%), OS (67.2% vs. 66.2%), or local recurrence (9% vs. 14.2%) between short-course radiotherapy or chemoradiation, respectively [103]. The Trans-Tasman Radiation Therapy Oncology Group 01.04 studied short-

Table 7.6 Trials of neoadjuvant chemoradiation with oxaliplatin

Trial	No. of patients	Radiotherapy regimen	Adjuvant chemo	pCR rate	Local recurrence	5-year disease-free survival	5-year overall survival	Grade III/IV adverse event rates
NSABP-R04 [88]	1608	50 Gy/28 Fx + Cape/5-FU vs. 50 Gy/28 Fx + Cape/5-FU + oxaliplatin	N/A	17.8% 19.5% ($p = 0.42$)	11.2% 12.1% ($p = 0.7$)	64.2% 69.2% ($p = 0.34$)	79% 81.3% ($p = 0.38$)	Diarrhea: 6.9% vs. 16.5%
CAO/ARO/AIO-04 [90]	1265	50 Gy/28 Fx + infusional 5-FU vs. 50 Gy/28 Fx + FOLFOX	5-FU vs. FOLFOX	13% need 17% ($p = 0.038$)	6% 3%	(3-year) 71.2% 75.9% ($p = 0.03$)	(3-year) 79% 81.3% ($p = 0.38$)	20% 24%
STAR-01 [91]	747	50 Gy/28 Fx + infusional 5-FU vs. 50 Gy/28 Fx + FOLFOX	5-FU based	16% 16% ($p = 0.904$)	NR	NR	NR	8% 24% ($p < 0.001$)
ACCORD 12/0405-Prodige 2 [92]	598	45 Gy/25 Fx or 50 Gy/25 Fx + capecitabine vs. RT + CapeOx	At discretion	13.9% 19.2% ($p = 0.09$)	6.1% 4.4% (ns)	(3-year) 67.9% 72.7% (ns)	(3-year) 87.6% 88.3% (ns)	10.9% 25.5% ($p < 0.001$)
PETACC-6 [93]	1094	45 Gy/25 Fx + capecitabine vs. 45 Gy/25 Fx + CapeOx	Capecitabine CapeOx	12% 14%	7.6% 4.6% ($p = 0.09$)	(3-year) 74.5% 73.9% ($p = 0.78$)	(3-year) 89.5% 87.4% ($p = 0.18$)	15% (GI 8%) 38% (GI 22%)

5-FU fluorouracil, *Cap*e capecitabine, *CapeOx* capecitabine + oxaliplatin, *FOLFOX* folinic acid + 5-FU + oxaliplatin, *Fx* fraction, *Gy* gray, *N/A* not applicable, *NR* not reported, *NS* not significant, *RT* radiation

Table 7.7 Trials of short-course radiotherapy and long-course chemoradiation

Trial	No. of patients	Treatment regimens	pCR rate	Local recurrence	Disease-free survival	Overall survival	Severe late toxicity rates
Swedish Rectal Cancer Trial [73]	1168	25 Gy/5 Fx preoperatively vs. Surgery alone	NR	9% 26% ($p < 0.001$)	(13-year f/u) 72% 62% ($p = 0.04$)	(13-year f/u) 38% 30% ($p = 0.008$)	NR
DCCG TME study [102]	1861	25 Gy/5 Fx preoperatively vs. Surgery alone	NR	5% 11% ($p < 0.0001$)	NR	(10-year) 48% 49%	NR
MRC CR-07 [80]	1350	25 Gy/5 Fx preoperatively vs. Surgery with selective CRT: 45 Gy/25 Fx + 5-FU	NR	4.7% 11.5% ($p < 0.0001$)	(5-year) 73.6% 66.7% ($p = 0.013$)	(5-year) 70.3% 67.9% ($p = 0.4$)	NR
Polish study [103]	316	25 Gy/5 Fx vs. 50 Gy/28 Fx + 5-FU + LV	NR	9% 4.2% ($p = 0.17$)	(4-year) 31.4% 34.6% ($p = 0.54$)	(4-year) 67.2% 66.2% ($p = 0.96$)	10.1% 7%
TROG 01.04 [104]	326	25 Gy/5 Fx vs. 50 Gy/28 Fx + CIVI 5-FU	1% 15% ($p < 0.001$)	7.5% 4.4% ($p = 0.25$)	NR	(5-year) 74% 70% ($p = 0.62$)	5.8% 8.2% ($p = 0.53$)

5-FU fluorouracil, *Cape* capecitabine, *CapeOx* capecitabine + oxaliplatin, *CRT* chemoradiation, *FOLFOX* folinic acid + 5-FU + oxaliplatin, *Fx* fraction, *f/u* follow-up, *Gy* gray, *LV* leucovorin, *N/A* not applicable, *NR* not reported, *NS* not significant

course radiotherapy vs. long-course chemoradiation with infusion 5-FU (225 mg/m^2/day, 7 days per week), randomizing 326 patients with T3 and N+ tumors. Adjuvant chemotherapy (5-FU 425 mg/m^2/day and LV 20 mg/m^2/day, days 1–5 of a 28-day cycle) was administered for 6 months in both arms. There was a higher proportion of low rectal tumors (<5 cm from anal verge) randomized to the short-course arm. A greater degree of downstaging was seen with chemoradiation—the proportion of ypT0–2 tumors was 45% vs. 28% posttherapy. Margins were similarly negative in the vast majority of both arms. Despite this, there were no clear differences in 5-year local recurrence rates (7.5% vs. 4.4%), DFS (30% vs. 27%), or OS (74% vs. 70%) for short-course radiotherapy or long-course chemoradiation, respectively. There was a numerically higher rate of local recurrences in distal rectal tumors, at 13% (6/48) with short course versus 3% (1/31) with chemoradiation, though this was not statistically significant. Importantly, late toxicity was no different between the two regimens [104].

In brief, short-course radiation is a viable option when considering preoperative therapy for locally advanced rectal cancers. There is evidence of less tumor regression and downstaging. This is often cited as a factor in choosing long-course chemoradiation. In studies of short-course radiotherapy, surgery has typically been conducted immediately on the heels treatment, within 7 days. When considering squamous cell carcinomas of the anus, responses can evolve over months following chemoradiation; similarly, retrospective data have suggested a greater rate of pathologic complete response when surgery is delayed from the standard 6–8 weeks to a slightly longer interval after completing chemoradiation [105]. With this in mind, one area of ongoing investigation is evaluating the role of delaying surgery after either radiotherapy approach, in hope of maximizing pathologic response. A greater interval to surgery might increase degree of downstaging with short-course radiotherapy. For now, it remains unclear whether such an approach is truly of benefit with respect to long-term outcomes.

Adjuvant Chemotherapy

Adjuvant chemotherapy is currently considered a standard component of perioperative therapy for locally advanced rectal cancer. It is administered in the majority of US patients and a recommendation on the NCCN guidelines, with fluoropyrimidine and oxaliplatin-based therapy, FOLFOX or CapeOx, being the preferred regimen [106, 107]. There is clear supportive data for adjuvant therapy in colon cancer [108, 109]. However, the data to support this practice in rectal cancer are slightly more murky.

5-FU-Based Adjuvant Therapy

The early GITSG and NCCTG studies demonstrated a survival benefit when radiotherapy was joined with concurrent or adjuvant chemotherapy [75, 80]. NSABP R-01 demonstrated a survival benefit with adjuvant chemotherapy in the absence of radiation [72]. A 2012 Cochrane analysis of 21 randomized controlled trials supported adjuvant 5-FU-based therapy in rectal cancer, suggesting a relative reduction in the

Table 7.8 Key trials of adjuvant therapy in rectal cancer

Trial	Patients	Inclusion criteria	Preoperative regimen	Adjuvant regimens	Disease-free survival	Overall survival
EORTC 22921[65]	1011	T3/T4, ≤15 cm from anal verge	Preoperative chemoRT or preoperative RT	Bolus 5-FU vs. Observation	(10-year) 47% 43.7% ($p = 0.29$)	(10-year) 51.8% 48.4% ($p = 0.32$)
Italian [111] I-CNR-RT	655	T3/4 or node positive, ≤15 cm from anal verge	ChemoRT + bolus 5-FU	Bolus 5-FU × 6 months vs. Observation	(5-year) 63.6% 60.8% ($p = 0.416$)	(5-year) 66.9% 67.9% ($p = 0.879$)
Dutch [112] PROCTOR/ SCRIPT	470 (closed early)	ypT3/4 or ypN+ after chemoradiation and TME	RT—25 Gy/5 Fx or chemoRT—45–50 Gy/25–28 Fx + 5-FU	Either bolus 5-FU or capecitabine vs. Observation	(5-year) 62.7% 55.4% ($p = 0.11$)	(5-year) 80.4% 79.2% ($p = 0.73$)
CAO/ARO/ AIO-04[90]	1265	T3/T4 or N+, ≤12 cm from anal verge	ChemoRT with 5-FU/ capecitabine vs. ChemoRT with FOLFOX/ CapeOx	FOLFOX/CapeOx vs. Infusional 5-FU/ capecitabine	(3-year) 75.9% 71.2% ($p = 0.03$)	(3-year) 81.3% 79% ($p = 0.38$)
PETACC-6 [93]	1094	T3/T4 or N+, ≤12 cm from anal verge	ChemoRT + capecitabine vs. ChemoRT + CapeOx	CapeOx vs. Capecitabine	(3-year) 74.5% 73.9% ($p = 0.78$)	(3-year) 89.5% 87.4% ($p = 0.18$)
CHRONICLE [113]	113 (closed early)	Rectal adenocarcinoma ≤15 cm from anal verge	Fluoropyrimidine-based chemoRT	CapeOx vs. Observation	(3-year) 78% 71% ($p = 0.56$)	(3-year) 89% 88% ($p = 0.75$)
ADORE [82]	321	ypT3–4 or ypN+ after chemoradiation and TME, ≤12 cm from anal verge	Fluoropyrimidine-based chemoRT	FOLFOX vs. 5-FU	(3-year) 71.6% 62.9% ($p = 0.047$)	(3-year) 95% 85.7% ($p = 0.036$)

5-FU fluorouracil, *Cape* capecitabine, *CapeOx* capecitabine + oxaliplatin, *ChemoRT* chemoradiation, *FOLFOX* folinic acid + 5-FU + oxaliplatin, *Fx* fraction, *Gy* gray, *LV* leucovorin, *N/A* not applicable, *NR* not reported, *NS* not significant, *TME* transmesorectal excision

risk of recurrence of 25% [110]. However, the conduct of multiple individual randomized studies in stage II and III rectal cancer has failed to demonstrate a clear, consistent benefit in the setting of the current standard: neoadjuvant therapy.

As previously mentioned, EORTC 22921 randomized 1011 patients to preoperative chemoradiation vs. radiation alone as well as adjuvant bolus 5-FU versus observation. 5-FU was administered as a daily bolus (350 mg/m^2/day) in combination with LV (20 mg/m^2/day) for 5 days, repeated every 3 weeks for a total of 4 cycles. The rate of adherence to preoperative chemoradiotherapy was 82% and to adjuvant chemotherapy just 43%; 27% of patients assigned to adjuvant therapy never began treatment [83]. In long-term follow-up, there was no statistical difference in 10-year DFS (47% vs. 43.7%) or OS (51.8 vs. 48.4) between adjuvant chemotherapy and observation, respectively [64]. The effect of low adherence rates following preoperative therapy and a somewhat more toxic 5-FU regimen may have obscured a difference between the arms—a particularly plausible explanation if the true difference is a modest one.

Additional modern randomized studies have similarly failed to demonstrate a clear benefit for 5-FU-based adjuvant therapy in locally advanced rectal cancer (Table 7.8) [65, 82, 90, 93, 111–113]. The Italian I-CNR-RT study randomized 655 patients with clinical T3/4 rectal cancer treated with neoadjuvant chemoradiation and surgery to adjuvant therapy with 5-FU (350 mg/m^2/day × 5 days, every 28 days × 6 cycles) and LV (10 mg/m^2/day × 5 days, every cycle). Similar to the EORTC study, 28% of patients randomized to adjuvant chemotherapy never began therapy and an additional 13.5% only received 2 cycles, such that just over 58% of patients completed 3–6 cycles of adjuvant chemotherapy. Disease-free and overall survival was no different between the two arms [111].

The Dutch PROCTOR/SCRIPT trial was designed to look at adjuvant chemotherapy with 5-FU or capecitabine in patients undergoing preoperative therapy (short-course radiotherapy or chemoradiation) and resection. One of two bolus 5-FU regimens or capecitabine (1250 mg/m^2 BID, days 1–14, every 21 days) was utilized, administered for roughly 6-month duration. The study was powered to detect a 10% improve-

ment in 5-year OS (60–70%), requiring 840 patients to achieve 90% power. Due to slow accrual, only 470 patients were accrued, of which only 437 were eligible for analysis. Of the patients, 73.6% completed all chemotherapy cycles. At a median 5-year follow-up, there was no significant difference in OS (nearly 80% in both groups). There was an absolute difference in DFS of 7% (62.7% vs. 55.4%, $p = 0.11$) favoring adjuvant chemotherapy, a trend that did not reach statistical significance. However, the study was underpowered to detect a difference of this magnitude [112].

Role of Oxaliplatin in Adjuvant Chemotherapy

Oxaliplatin has been studied in multiple locally advanced rectal cancer studies, though much of the data are immature with respect to long-term survival. Results to date have been conflicting. CAO/ARO/AIO-04 and PETACC-6 are both large trials that randomized patients to a preoperative regimen of radiotherapy with capecitabine +/− oxaliplatin. Postoperatively, patients received the same adjuvant chemotherapy regimens: capecitabine +/− oxaliplatin. More than 80% of patients received all of the planned cycles of adjuvant therapy [90]. Final results of CAO/ARO/AIO-4 have recently been published. At a median follow-up of 50 months, the 3-year DFS was improved with oxaliplatin (75.9% vs. 71.2%). No difference in survival was observed [94]. The long-term results of PETACC-6 have not yet been published. However, data presented at the European Society for Medical Oncology (ESMO) 2016 Congress demonstrated no difference between the arms, with a median follow-up of 52 months. As in other rectal trials, the ability to routinely administer adjuvant chemotherapy was fair at best [114]. After preoperative radiotherapy with capecitabine and oxaliplatin, in the oxaliplatin arm, only 75% of patients initiated adjuvant chemotherapy, with 65% of the total receiving oxaliplatin and only 57% completing all planned cycles [93].

Two smaller studies have also examined the question of adjuvant oxaliplatin after fluoropyrimidine-based chemoradiotherapy. The CHRONICLE study randomized rectal cancer patients to postoperative capecitabine and oxaliplatin or observation. Of 93% of patients who began chemotherapy, only 48% completed the planned 6 cycles. Ultimately, only 113 of the planned 800 patients were accrued, and the study was closed early. Three-year DFS was 78% with chemotherapy vs. 71% with surgery alone, which was not statistically different ($p = 0.53$). The OS was identical [113]. On the other hand, ADORE was a phase II randomized study, comparing 4 months of adjuvant 5-FU to FOLFOX in a Korean population with pathologic stage II/III rectal cancer after neoadjuvant therapy. This study examined a higher risk population (i.e., ypT3 or ypN+)—a group with greater potential to recur and thus possibly greater potential benefit from adjuvant therapy. More than 95% of patients completed all planned cycles of therapy. At a median of 38-month follow-up, the median 3-year DFS was improved at 71.6% vs. 62.9% with the addition of oxaliplatin. Toxicity was greater, as expected, though the rate of severe adverse events was no different [115].

Thus, the data remain inconclusive at this point as to the true benefit for oxaliplatin as adjuvant therapy in rectal cancer. Moreover, the adjuvant data in general remain inconsistent, potentially stemming from inclusion of mixed populations—specifically a substantial proportion of patients who at relatively lesser risk of recurrence hampers detection of benefit. Pretherapy staging is imperfect in assessing nodal stage, with the sensitivity of MRI estimated at 77% and specificity at 71% [116]; essentially, small involved perirectal lymph nodes can be called benign in nearly one of four cases and larger reactive nodes can be called malignant in greater than a third of cases. As suggested by the phase II ADORE, patients at higher risk may be the ones who are best served by adjuvant oxaliplatin. On the other hand, those patients who achieve a pathologic complete response have excellent long-term outcomes on the whole [117]. At this time, there are no definitive data to guide decisions, nor as to whether pathologic stage should trump clinical stage in guiding therapy. In line with guidelines, adjuvant therapy is recommended in fit patients, with both fluoropyrimidines alone and in combination with oxaliplatin being reasonable options.

Neoadjuvant Chemotherapy

As evidenced by the prior discussion, in rectal cancer substantial difficulties may prohibit administration of full planned adjuvant chemotherapy following neoadjuvant pelvic chemoradiation and surgical resection. In an analysis of the SEER database, greater than one in three patients did not receive postoperative chemotherapy [118]. At this point, with surgical and radiotherapy advances, the major risk in locally advanced rectal cancer is that of distant, rather than local, recurrence. As survival gains with neoadjuvant radiotherapy are not reliably reproducible in modern studies and chemotherapy regimens have dramatically improved, interest has grown in the administration of neoadjuvant chemotherapy for patients with locally advanced rectal cancer. A small pilot study examined the administration of preoperative FOLFOX—6 cycles, the first 4 also with Avastin—in 32 patients with stages II and III rectal cancer. Tumor regression was seen in all patients with a pCR rate of 25% and no local recurrences at 4 years [119]. These data have supported the initiation of the cooperative group study, PROSPECT (N1048, NCT01515787). This study is randomizing patients with nonbulky locally advanced rectal cancer to neoadjuvant chemoradiation or 6 cycles of neoadjuvant FOLFOX. Patients in the chemotherapy arm with response to therapy will forgo chemoradiation and proceed straight to surgery. The primary endpoint is disease-free survival.

Taking this a step further, other investigators have examined utilization of multiple modalities preoperatively, in hope of achieving maximal downstaging of the tumor and reducing systemic recurrence risk more effectively through the early administration of full-dose systemic therapy. The CONTRE study treated 39 patients with stages II and III rectal cancer with 8 cycles of neoadjuvant FOLFOX, followed by chemoradiation with capecitabine and surgical resection. Pathologic complete response was achieved in 33% of patients (13/39) [120]. Another recently reported multicenter nonrandomized phase II study treated patients with stage II or III rectal cancer via a regimen of neoadjuvant chemotherapy followed by a variable number of cycles of preoperative FOLFOX in the four arms: 0, 2, 4, or 6. On analysis of the 259 evaluable patients, there was clear evidence of increased pathologic downstaging with a greater amount of preoperative chemotherapy. Pathologic complete response increased with each additional 2 cycles of chemotherapy, with pCR rates standing at 18%, 25%, 30%, and 38%. No evidence of increased surgical complications was noted [121]. Key trials of neoadjuvant therapy are depicted in Table 7.8 [65, 82, 90, 93, 111–113].

Though pathologic complete response is linked to better long-term outcomes in locally advanced rectal cancer, at this time, in the trial setting, it is not clear that pCR rate is an adequate surrogate for overall survival. In any study, the pCR rate achieved shows clear relation to the initial stage of the tumor in question. This can create marked intertrial variability on its own. In any case, multiple permutations of this neoadjuvant approach are currently under active investigation in hope of improving outcomes and lessening toxicity for patients.

Adjuvant Therapy for Resectable Metastatic Colorectal Cancer

Colorectal cancer patients with oligometastatic disease can achieve prolonged PFS, prolonged OS, as well as a possible cure with metastasectomy. Indeed, the 5-year OS from modern series of patients with hepatic resection exceeds 50% and compares favorably to a historic control of 10% 5-year survival for patients treated with systemic chemotherapy [122–128]. Similar favorable overall 5-year survival rates have been described for patients undergoing pulmonary metastasectomy [129]. However, one of the main challenges of patients with hepatic and lung metastases resection is disease recurrence. It is estimated that approximately 70% of patients with hepatic resection for colorectal liver metastases will have disease recurrence within 3 years from surgery, and only 20% of patients with hepatic resection are estimated to achieve a curative outcome [122, 130]. Given the considerable risk of disease recurrence in patients with hepatic and lung resection, efforts have been placed on developing adjuvant strategies in these populations. To date, randomized studies have been completed and reported on patients with hepatic metastasectomy, while recommendations regarding patients with pulmonary metastases resection are based predominantly on extrapolation from the liver resection data and/or on outcome data from larger retrospective series.

Systemic Therapy in the Adjuvant Treatment After Resection of Colorectal Liver Metastases

The FFCD 9002 phase III clinical trial evaluated the impact of 6 months of adjuvant 5-FU/LV following hepatic metastases resection [131]. Patients were required to have no evidence of local recurrence or other extrahepatic metastatic disease and to have undergone an R0 resection of hepatic metastases. In addition, the receipt of any chemotherapy within 1 year prior to enrollment was considered an exclusion criteria. After adjusting for major prognostic factors, patients on the chemotherapy arm were more likely to be disease free at 5 years than the observation arm (33.5% vs. 26.7%; $p = 0.028$). Treatment with chemotherapy was associated with a trend toward an improved 5-year OS (51.1% vs. 41.1%), which did not reach statistical significance. The Canadian and European Intergroup randomized patients with resected colorectal lung or liver metastases to observation or 6 months of 5-FU/LV, and patients did not show any improvement in DFS or OS [132]. A subsequent pooled analysis of both studies (278 patients) suggested a strong trend for an improvement in favor of chemotherapy in disease-free survival (HR = 1.32; $p = 0.058$) and overall survival (HR = 1.32; $p = 0.095$) [132]. The lack of statistical significance is in part related to an underpowered sample size. A more recent clinical trial investigated 6 months of UFT/LV vs. observation in 180 patients after hepatic colorectal cancer metastases resection. The UFT/LV arm had a significant reduction in RFS (3-year RFS 38.6% vs. 32.3%; $p = 0.003$), but this did not translate into a difference in overall survival [133]. These data point to a potential clinical benefit from fluoropyrimidine in the adjuvant treatment of resected colorectal liver metastases, at least in patients with no or limited prior systemic therapy. Further intensification of chemotherapy beyond fluoropyrimidine monotherapy in the adjuvant or neoadjuvant settings has led to mixed conclusions. The CPT-GMA-301 adjuvant trial investigated the combination FOLFIRI vs. 5-FU/LV control in patients with resected hepatic metastases [134]. Prior chemotherapy was allowed with the exception of irinotecan. Despite the large sample size of this study ($n = 306$), no difference was noted in disease-free survival between the FOLFIRI and 5-FU/LV arms. These findings are in line with other adjuvant clinical trials in stage III disease where irinotecan did not improve the disease outcome in comparison to 5-FU/LV [25–27]. On the other hand, the addition of oxaliplatin in the neoadjuvant setting has been linked to beneficial reductions in recurrence rate as described as follows [130].

Systemic Therapy in the Neoadjuvant Treatment of Resectable Hepatic Colorectal Cancer Metastases

The EORTC 40983 study randomized patients with four or less hepatic colorectal metastases to perioperative FOLFOX chemotherapy or observation [130]. Patients were randomized to 3 months of FOLFOX chemotherapy followed by hepatic resection and another 3 months of FOLFOX vs. hepatic resection alone. The primary endpoint of 3-year DFS rate in the eligible population was 36.2% vs. 28.1%, favoring perioperative chemotherapy (HR = 0.77; p = 0.041). This translated into a statistically insignificant trend in improvement in OS on the FOLFOX arm (5-year OS = 51.2%) vs. observation (5-year OS = 47.8%). While this study confirms a clinical advantage to perioperative FOLFOX chemotherapy in resectable hepatic colorectal metastases, it does not provide any guidance to the additional benefits of FOLFOX in comparison to 5-FU, nor does it confirm a benefit for a neoadjuvant strategy vs. an adjuvant strategy.

The role of cetuximab as part of a neoadjuvant chemotherapy regimen in resectable colorectal liver metastases was investigated through the New EPOC trial [135]. Patients with resectable or suboptimally resectable *KRAS* wild-type colorectal liver metastases were randomized to perioperative chemotherapy (fluoropyrimidine plus oxaliplatin or fluoropyrimidine plus irinotecan) with or without cetuximab. The PFS was significantly shorter in the cetuximab arm (14.1 vs. 20.5 months; HR = 1.48 with a 95% CI: 1.04–2.12). The detrimental impact of cetuximab on the New EPOC trial is also consistent with other data pointing to a lack of benefit from cetuximab in the adjuvant treatment of stage III colorectal cancer [33, 35]. The use of anti-EGFR therapy in the neoadjuvant or adjuvant treatment of resectable metastatic colorectal cancer is not recommended at this time, even when considering patients with *RAS* wild-type tumors. While no dedicated randomized phase III clinical trials have explored the role of anti-angiogenic therapy in the neoadjuvant treatment of resectable hepatic metastases, multiple phase III studies failed to show a benefit for bevacizumab in stage III disease [28–31]. Therefore, the integration of anti-angiogenic therapy with chemotherapy in the adjuvant and neoadjuvant treatment of resectable liver metastases is not indicated at this time.

Combination of Adjuvant Systemic and Regional Therapy Following Hepatic Colorectal Metastases Resection

Given the increased risk of liver recurrence posthepatectomy, several studies have explored the addition of regional therapy to systemic therapy following metastasectomy. A phase III clinical trial investigated a combination of 5-FU/LV alternating with hepatic arterial infusion (HAI) of FUDR (6 × 5-week cycles) vs. 5-FU/LV alone (6 × 4-week cycles) in 156 patients with complete resection of hepatic colorectal metastases [136]. Patients receiving the HAI + systemic combination experienced an improved 2-year hepatic disease-free survival (90% vs. 60%; $p < 0.0001$) and 2-year survival (HR = 2.34; $p = 0.027$). A 10-year study update further confirms an advantage of the combination therapy in terms of progression-free survival, hepatic disease-free survival, and 10-year survival rate (38.7% vs. 16.3%) [137]. Another smaller randomized study evaluated the combination of continuous infusion 5-FU and HAI of FUDR vs. continuous infusion 5-FU in patients with 1–3 resected hepatic metastases [138]. Patients receiving the combination therapy experience an improved hepatic DFS (67% vs. 43%; $p = 0.03$) and 4-year recurrence-free survival (46% vs. 25%; p = 0.04). These results suggest a significant impact of regional therapy on hepatic disease recurrence, especially in patients with high risk of disease recurrence. Both studies were underpowered to show a survival advantage; however, a trend in improved survival was noted—especially in high-risk patients [137]. Additional studies have recently investigated combinations of HAI with more modern systemic therapy such as FOLFOX or FOLFIRI with promising results [139, 140]. However, none of these combinations have been validated in definitive randomized phase III clinical trials.

Adjuvant Therapy for Resected Pulmonary Metastases

There is a paucity of prospective data on the value of systemic chemotherapy in patients with curative-intent lung metastasectomy. Retrospective series suggest that the outcome of patients with resection of pulmonary metastases has a favorable overall survival with median survival exceeding 5 years [129]. Several small retrospective studies and a large meta-analysis did not support a benefit from adjuvant chemotherapy post pulmonary colorectal metastases resection [129, 141–143]. Alternatively, other retrospective series have reported an improvement in disease-free survival but no improvement in associated overall survival [144]. The interpretation of these studies and other retrospective series is limited by patient heterogeneity, treatment selection bias, and adequate quality data control. Despite the limitation of the existing data, it is generally recommended that patients with pulmonary metastases receive some form of adjuvant systemic chemotherapy, especially in settings where patients had limited prior systemic therapy exposure. Such recommendations are based on extrapolations from the hepatic resection data. The optimal chemotherapy regimen in such settings is not well defined. In general, 6 months of the projected most effective combination therapy is considered.

In short, perioperative and adjuvant treatment strategies have been developed to improve upon the high rates of disease recurrence following hepatic resection for colorectal liver metastases. Adjuvant 5-FU/LV, perioperative FOLFOX, or adjuvant systemic 5-FU + HAI FUDR have all shown to

improve DFS in resected colorectal liver metastases. Data are more limited for adjuvant therapy in resected colorectal pulmonary metastases and are generally extrapolated from hepatic resection data, but 6 months of the projected most effective combination therapy in the adjuvant setting should be considered. The choice of adjuvant or perioperative strategy is dependent on expected patient tolerance, institutional experience with HAI therapy, and multidisciplinary panel recommendations.

References

1. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):104–17.
2. Fakih MG. Metastatic colorectal cancer: current state and future directions. J Clin Oncol. 2015;33(16):1809–24.
3. Dienstmann R, Salazar R, Tabernero J. Personalizing colon cancer adjuvant therapy: selecting optimal treatments for individual patients. J Clin Oncol. 2015;33:1787–96.
4. Chen VW, Hsieh MC, Charlton ME, Ruiz BA, Karlitz J, Altekruse SF, et al. Analysis of stage and clinical/prognostic factors for colon and rectal cancer from SEER registries: AJCC and collaborative stage data collection system. Cancer. 2014;120:3793–806.
5. Hari DM, Leung AM, Lee JH, Sim MS, Vuong B, Chiu CG, et al. AJCC cancer staging manual 7th edition criteria for colon cancer: do the complex modifications improve prognostic assessment? J Am Coll Surg. 2013;217:181–90.
6. Anonymous. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA. 1990;264:1444–50.
7. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer. Why we still don't know. JAMA. 1988;259:3571–8.
8. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med. 1995;122:321–6.
9. Wolmark N, Rockette H, Fisher B, Wickerham DL, Redmond C, Fisher ER, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from national surgical adjuvant breast and bowel project protocol c-03. J Clin Oncol. 1993;11:1879–87.
10. Wolmark N, Rockette H, Mamounas E, Jones J, Wieand S, Wickerham DL, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with dukes' b and c carcinoma of the colon: results from national surgical adjuvant breast and bowel project c-04. J Clin Oncol. 1999;17:3553–9.
11. Arkenau HT, Bermann A, Rettig K, Strohmeyer G, Porschen R, Onkologie AG. 5-fluorouracil plus leucovorin is an effective adjuvant chemotherapy in curatively resected stage III colon cancer: long-term follow-up results of the adjcca-01 trial. Ann Oncol. 2003;14:395–9.
12. Haller DG, Catalano PJ, Macdonald JS, O'Rourke MA, Frontiera MS, Jackson DV, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of intergroup 0089. J Clin Oncol. 2005;23:8671–8.
13. Lembersky BC, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from national surgical adjuvant breast and bowel project protocol c-06. J Clin Oncol. 2006;24:2059–64.
14. Twelves C, Wong A, Nowacki MP, Abt M, Burris H, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352:2696–704.
15. Wolmark N, Colangelo L, Wieand S. National surgical adjuvant breast and bowel project trials in colon cancer. Semin Oncol. 2001;28:9–13.
16. Smith RE, Colangelo L, Wieand HS, Begovic M, Wolmark N. Randomized trial of adjuvant therapy in colon carcinoma: 10-year results of nsabp protocol c-01. J Natl Cancer Inst. 2004;96:1128–32.
17. Wolmark N, Rockette H, Wickerham DL, Fisher B, Redmond C, Fisher ER, et al. Adjuvant therapy of dukes' a, b, and c adenocarcinoma of the colon with portal-vein fluorouracil hepatic infusion: preliminary results of national surgical adjuvant breast and bowel project protocol c-02. J Clin Oncol. 1979;8:1466–75.
18. Köhne CH, Bedenne L, Carrato A, Bouché O, Popov I, Gaspà L, et al. A randomised phase III intergroup trial comparing high-dose infusional 5-fluorouracil with or without folinic acid with standard bolus 5-fluorouracil/folinic acid in the adjuvant treatment of stage III colon cancer: the Pan-European trial in adjuvant colon cancer 2 study. Eur J Cancer. 2013;49:1868–75.
19. Andre T, Colin P, Louvet C, Gamelin E, Bouche O, Achille E, et al. Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: results of a randomized trial. J Clin Oncol. 2003;21(15):2896–903.
20. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350:2343–51.
21. André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol. 2015;33(35):4176–87. https://doi.org/10.1200/JCO.2015.63.4238.
22. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from nsabp c-07. J Clin Oncol. 2007;25:2198–204.
23. Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of nsabp c-07 trial, including survival and subset analyses. J Clin Oncol. 2011;29:3768–74.
24. Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the no16968 randomized controlled phase III trial. J Clin Oncol. 2015;33:3733–40.
25. Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol. 2007;25:3456–61.
26. Van Cutsem E, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: Petacc-3. J Clin Oncol. 2009;27:3117–25.
27. Ychou M, Raoul JL, Douillard JY, Gourgou-Bourgade S, Bugat R, Mineur L, et al. A phase III randomised trial of lv5fu2 + irinotecan versus lv5fu2 alone in adjuvant high-risk colon cancer (FNCLCC ACCORD02/FFCD9802). Ann Oncol. 2009;20:674–80.
28. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of nsabp protocol c-08. J Clin Oncol. 2011;29:11–6.

29. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Lopa SH, et al. Bevacizumab in stage II–III colon cancer: 5-year update of the national surgical adjuvant breast and bowel project c-08 trial. J Clin Oncol. 2013;31(3):359–64.
30. Pogue-Geile KL, Yothers G, Taniyama Y, Tanaka N, Gavin P, Colangelo L, et al. Defective mismatch repair and benefit from bevacizumab for colon cancer: findings from nsabp c-08. J Natl Cancer Inst. 2013;105:989–92.
31. de Gramont A, Van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol. 2012;13:1225–33.
32. Midgley RS, Love S, Tomlinson I, Johnstone E, Scudder C, Pearson SR, et al. Final results from quasar2, a multicentre, international randomised phase III trial of capecitabine (CAP) +/− bevacizumab (BEV) in the adjuvant setting of stage II/III colorectal cancer (CRC). Ann Oncol. 2014;25 https://doi.org/10.1093/annonc/mdu1438.1010.
33. Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA. 2012;307:1383–93.
34. Huang J, Nair SG, Mahoney MR, Nelson GD, Shields AF, Chan E, et al. Comparison of FOLFIRI with or without cetuximab in patients with resected stage III colon cancer; NCCTG (alliance) intergroup trial n0147. Clin Colorectal Cancer. 2014;13:100–9.
35. Taieb J, Tabernero J, Mini E, Subtil F, Folprecht G, Van Laethem JL, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (petacc-8): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15:862–73.
36. Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. J Natl Cancer Inst. 2001;93:850–7.
37. Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med. 2001;345:1091–7.
38. Haller DG, O'Connell MJ, Cartwright TH, Twelves CJ, McKenna EF, Sun W, et al. Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized, controlled trials. Ann Oncol. 2015;26:715–24.
39. Gross CP, McAvay GJ, Guo Z, Tinetti ME. The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. Cancer. 2007;109:2410–9.
40. Muss HB, Biganzoli L, Sargent DJ, Aapro M. Adjuvant therapy in the elderly: making the right decision. J Clin Oncol. 2007;25:1870–5.
41. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, et al. Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/dukes' b2 colon cancer. J Clin Oncol. 1995;13:2936–43.
42. Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K, et al. Comparative efficacy of adjuvant chemotherapy in patients with dukes' b versus dukes' c colon cancer: results from four national surgical adjuvant breast and bowel project adjuvant studies (c-01, c-02, c-03, and c-04). J Clin Oncol. 1999;17:1349–55.
43. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. Efficacy of adjuvant fluorouracil and folinic acid in b2 colon cancer. J Clin Oncol. 1999;17:1356–63.
44. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet. 2007;370:2020–9.
45. Benson AB, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American society of clinical oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22:3408–19.
46. National Comprehensive Cancer Network. NCCN guidelines: colon cancer, version 2.2016. http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
47. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A national cancer institute workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998;58:5248–57.
48. Zaanan A, Fléjou JF, Emile JF, Des GG, Cuilliere-Dartigues P, Malka D, et al. Defective mismatch repair status as a prognostic biomarker of disease-free survival in stage III colon cancer patients treated with adjuvant FOLFOX chemotherapy. Clin Cancer Res. 2011;17:7470–8.
49. Des Guetz G, Lecaille C, Mariani P, Bennamoun M, Uzzan B, Nicolas P, et al. Prognostic impact of microsatellite instability in colorectal cancer patients treated with adjuvant FOLFOX. Anticancer Res. 2010;30:4297–301.
50. Gavin PG, Paik S, Yothers G, Pogue-Geile KL. Colon cancer mutation: prognosis/prediction-response. Clin Cancer Res. 2013;19:1301.
51. Tougeron D, Sickersen G, Lecomte T, Mouillet G, Trouilloud I, Coriat R, et al. Impact of adjuvant chemotherapy with 5-FU or FOLFOX in colon cancers with microsatellite instability: an AGEO multicenter study. J Clin Oncol. 2014;32:Abstract 3508.
52. Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28:3219–26.
53. You YN, Rustin RB, Sullivan JD. Oncotype dx(®) colon cancer assay for prediction of recurrence risk in patients with stage II and III colon cancer: a review of the evidence. Surg Oncol. 2015;24:61–6.
54. Gray RG, Quirke P, Handley K, Lopatin M, Magill L, Baehner FL, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. J Clin Oncol. 2011;29:4611–9.
55. Venook AP, Niedzwiecki D, Lopatin M, Ye X, Lee M, Friedman PN, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group b (CALGB) 9581. J Clin Oncol. 2013;31:1775–81.
56. Yothers G, O'Connell MJ, Lee M, Lopatin M, Clark-Langone KM, Millward C, et al. Validation of the 12-gene colon cancer recurrence score in nsabp c-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. J Clin Oncol. 2013;31:4512–9.
57. Srivastava G, Renfro LA, Behrens RJ, Lopatin M, Chao C, Soori GS, et al. Prospective multicenter study of the impact of oncotype dx colon cancer assay results on treatment recommendations in stage II colon cancer patients. Oncologist. 2014;19:492–7.
58. Sharif S, O'Connell MJ. Gene signatures in stage II colon cancer: a clinical review. Curr Colorectal Cancer Rep. 2012;8(3):225–31.
59. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
60. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst. [Guideline Practice Guideline Research Support, U.S. Gov't, P.H.S.]. 2001;93(8):583–96.
61. Pilipshen SJ, Heilweil M, Quan SH, Sternberg SS, Enker WE. Patterns of pelvic recurrence following definitive resections of rectal cancer. Cancer. [Comparative Study]. 1984;53(6):1354–62.

62. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. [Clinical Trial Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2001;345(9):638–46.
63. Schoellhammer HF, Gregorian AC, Sarkisyan GG, Petrie BA. How important is rigid proctosigmoidoscopy in localizing rectal cancer? Am J Surg. [Comparative Study]. 2008;196(6):904–8; discussion 908.
64. Muthusamy VR, Chang KJ. Optimal methods for staging rectal cancer. Clin Cancer Res. [Review]. 2007;13(22 Pt 2):6877s–84s.
65. Taylor FG, Quirke P, Heald RJ, Moran BJ, Blomqvist L, Swift IR, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the mercury study. J Clin Oncol. [Clinical Trial Research Support, Non-U.S. Gov't]. 2014;32(1):34–43.
66. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol. [Research Support, Non-U.S. Gov't Review]. 2008;26(2):303–12.
67. Havenga K, Enker WE, Norstein J, Moriya Y, Heald RJ, van Houwelingen HC, et al. Improved survival and local control after total mesorectal excision or d3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. Eur J Surg Oncol. [Multicenter Study]. 1999;25(4):368–74.
68. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. [Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2007;246(5):693–701.
69. den Dulk M, Putter H, Collette L, Marijnen CA, Folkesson J, Bosset JF, et al. The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer. Eur J Cancer. [Research Support, Non-U.S. Gov't]. 2009;45(7):1175–83.
70. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pt3 rectal carcinomas. Int J Colorectal Dis. 2001;16(5):298–304.
71. Merkel S, Weber K, Schellerer V, Gohl J, Fietkau R, Agaimy A, et al. Prognostic subdivision of ypt3 rectal tumours according to extension beyond the muscularis propria. Br J Surg. 2014;101(5):566–72.
72. Dresen RC, Peters EE, Rutten HJ, Nieuwenhuijzen GA, Demeyere TB, van den Brule AJ, et al. Local recurrence in rectal cancer can be predicted by histopathological factors. Eur J Surg Oncol. 2009;35(10):1071–7.
73. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg. [Comparative Study Research Support, Non-U.S. Gov't]. 2008;95(2):229–36.
74. Anonymous, Gastrointestinal tumor study group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med. [Clinical Trial Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S.]. 1985;312(23):1465–72.
75. Douglass HO Jr, Moertel CG, Mayer RJ, Thomas PR, Lindblad AS, Mittleman A, et al. Survival after postoperative combination treatment of rectal cancer. N Engl J Med. [Letter]. 1986;315(20):1294–5.
76. Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from nsabp protocol r-01. J Natl Cancer Inst. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 1988;80(1):21–9.
77. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S.]. 1991;324(11):709–15.
78. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. [Clinical Trial Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2004;351(17):1731–40.
79. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. [Clinical Trial, Phase III Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2012;30(16):1926–33.
80. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. [Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2009;373(9666):811–20.
81. Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet. [Research Support, Non-U.S. Gov't]. 2009;373(9666):821–8.
82. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in t3–4 rectal cancers: results of FFCD 9203. J Clin Oncol. [Multicenter Study Randomized Controlled Trial]. 2006;24(28):4620–5.
83. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. [Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2006;355(11):1114–23.
84. Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results–EORTC 22921. J Clin Oncol. [Clinical Trial Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2005;23(24):5620–7.
85. Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol. [Comparative Study Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2014;15(2):184–90.
86. O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med. [Clinical Trial Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S.]. 1994;331(8):502–7.
87. Smalley SR, Benedetti JK, Williamson SK, Robertson JM, Estes NC, Maher T, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol. [Clinical Trial, Phase III Randomized Controlled Trial Research Support, N.I.H., Extramural]. 2006;24(22):3542–7.
88. Allegra CJ, Yothers G, O'Connell MJ, Beart RW, Wozniak TF, Pitot HC, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase

III randomized clinical trial. J Natl Cancer Inst. [Clinical Trial, Phase III Randomized Controlled Trial Research Support, N.I.H., Extramural]. 2015;107(11):pii: djv248.
89. Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. [Clinical Trial, Phase III Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2012;13(6):579–88.
90. Rodel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol. [Clinical Trial, Phase III Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2012;13(7):679–87.
91. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the star-01 randomized phase III trial. J Clin Oncol. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial]. 2011;29(20):2773–80.
92. Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol. [Clinical Trial, Phase III Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2010;28(10):1638–44.
93. Schmoll HJ, Haustermans K, Price TJ, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: disease-free survival results at interim analysis. J Clin Oncol. 2014;32(15_suppl):abstr 3501.
94. Rodel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2015;16(8):979–89.
95. Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Lafay I, Hennequin C, Etienne PL, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol. [Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2012;30(36):4558–65.
96. Crane CH, Eng C, Feig BW, Das P, Skibber JM, Chang GJ, et al. Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. [Clinical Trial, Phase II Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2010;76(3):824–30.
97. Spigel DR, Bendell JC, McCleod M, Shipley DL, Arrowsmith E, Barnes EK, et al. Phase II study of bevacizumab and chemoradiation in the preoperative or adjuvant treatment of patients with stage II/III rectal cancer. Clin Colorectal Cancer. [Clinical Trial, Phase II Multicenter Study Research Support, Non-U.S. Gov't]. 2012;11(1):45–52.
98. Salazar R, Capdevila J, Laquente B, Manzano JL, Pericay C, Villacampa MM, et al. A randomized phase II study of capecitabine-based chemoradiation with or without bevacizumab in resectable locally advanced rectal cancer: clinical and biological features. BMC Cancer. 2015;15:60.
99. Landry JC, Feng Y, Prabhu RS, Cohen SJ, Staley CA, Whittington R, et al. Phase II trial of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: 5-year clinical outcomes ECOG-ACRIN cancer research group e3204. Oncologist. 2015;20(6):615–6.
100. Sclafani F, Gonzalez D, Cunningham D, Hulkki Wilson S, Peckitt C, Giralt J, et al. RAS mutations and cetuximab in locally advanced rectal cancer: results of the EXPERT-C trial. Eur J Cancer. [Clinical Trial, Phase II Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2014;50(8):1430–6.
101. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol. [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2005;23(24):5644–50.
102. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. [Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2011;12(6):575–82.
103. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. [Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2006;93(10):1215–23.
104. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with t3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol. [Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2012;30(31):3827–33.
105. Sloothaak DA, Geijsen DE, van Leersum NJ, Punt CJ, Buskens CJ, Bemelman WA, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg. 2013;100(7):933–9.
106. Khrizman P, Niland JC, ter Veer A, Milne D, Bullard Dunn K, Carson WE 3rd, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvant therapy: a national comprehensive cancer network analysis. J Clin Oncol. 2013;31(1):30–8.
107. Benson AB 3rd, Venook AP, Bekaii-Saab T, Chan E, Chen YJ, Cooper HS, et al. Rectal cancer, version 2.2015. J National Compr Cancer Network: JNCCN. [Research Support, Non-U.S. Gov't]. 2015;13(6):719–28; quiz 728.
108. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the mosaic trial. J Clin Oncol. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2009;27(19):3109–16.
109. Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the no16968 randomized controlled phase III trial. J Clin Oncol. 2015;33(32):3733–40.
110. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev. [Meta-Analysis Review]. 2012;3:CD004078.

111. Sainato A, Cernusco Luna Nunzia V, Valentini V, De Paoli A, Maurizi ER, Lupattelli M, et al. No benefit of adjuvant fluorouracil leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). Radiother Oncol. [Clinical Trial, Phase III Randomized Controlled Trial]. 2014;113(2):223–9.
112. Breugom AJ, van Gijn W, Muller EW, Berglund A, van den Broek CB, Fokstuen T, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch colorectal cancer group (DCCG) randomized phase III trial. Ann Oncol. [Research Support, Non--U.S. Gov't]. 2015;26(4):696–701.
113. Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. Ann Oncol. [Clinical Trial, Phase III Randomized Controlled Trial Research Support, Non--U.S. Gov't]. 2014;25(7):1356–62.
114. Schmoll HJSA, Hofheinz RD, Price TJ, Nordlinger B, Daisne J-F, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin vs. Capecitabine alone in locally advanced rectal cancer: final analyses. Ann Oncol. 2016;27(suppl 6):467PD.
115. Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (adore): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol. [Clinical Trial, Phase II Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non--U.S. Gov't]. 2014;15(11):1245–53.
116. Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, et al. Diagnostic accuracy of MRI for assessment of t category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol. [Meta-Analysis Research Support, Non-U.S. Gov't]. 2012;19(7):2212–23.
117. Zorcolo L, Rosman AS, Restivo A, Pisano M, Nigri GR, Fancellu A, et al. Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis. Ann Surg Oncol. [Meta-Analysis]. 2012;19(9):2822–32.
118. Haynes AB, You YN, Hu CY, Eng C, Kopetz ES, Rodriguez-Bigas MA, et al. Postoperative chemotherapy use after neoadjuvant chemoradiotherapy for rectal cancer: analysis of surveillance, epidemiology, and end results-Medicare data, 1998–2007. Cancer. [Research Support, N.I.H., Extramural]. 2014;120(8):1162–70.
119. Schrag D, Weiser MR, Goodman KA, Gonen M, Hollywood E, Cercek A, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol. [Clinical Trial, Phase II Research Support, Non-U.S. Gov't]. 2014;32(6):513–8.
120. Perez K, Safran H, Sikov W, Vrees M, Klipfel A, Shah N, et al. Complete neoadjuvant treatment for rectal cancer: the brown university oncology group CONTRE study. Am J Clin Oncol. 2017;40(3):283–7.
121. Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Effect of adding mfolfox6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. [Clinical Trial, Phase II Multicenter Study Research Support, N.I.H., Extramural]. 2015;16(8):957–66.
122. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25(29):4575–80.
123. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235(6):759–66.
124. Wei AC, Greig PD, Grant D, Taylor B, Langer B, Gallinger S. Survival after hepatic resection for colorectal metastases: a 10-year experience. Ann Surg Oncol. 2006;13(5):668–76.
125. Pawlik TM, Vauthey JN, Abdalla EK, Pollock RE, Ellis LM, Curley SA. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. Arch Surg. 2006;141(6):537–43; discussion 543–4.
126. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with f-18 fluorodeoxyglucose (FDG-PET). Ann Surg. 2004;240(3):438–47; discussion 447–50.
127. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239(6):818–25; discussion 825–7.
128. Sanoff HK, Sargent DJ, Campbell ME, Morton RF, Fuchs CS, Ramanathan RK, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. J Clin Oncol. 2008;26(35):5721–7.
129. Salah S, Watanabe K, Welter S, Park JS, Park JW, Zabaleta J, et al. Colorectal cancer pulmonary oligometastases: pooled analysis and construction of a clinical lung metastasectomy prognostic model. Ann Oncol. 2012;23(10):2649–55.
130. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with folfox4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371(9617):1007–16.
131. Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol. 2006;24(31):4976–82.
132. Mitry E, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008;26(30):4906–11.
133. Kobayashi A, Hasegawa K, Saiura A, Takayama T, Miyagawa S, Yamamoto J, et al. A randomized controlled trial evaluating efficacy of adjuvant oral uracil-tegafur (UFT) with leucovorin (LV) after resection of colorectal cancer liver metastases: the UFT/LV study. J Clin Oncol. 2014;32(5s_ Suppl):abstr 3584.
134. Ychou M, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol. 2009;20(12):1964–70.
135. Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the new EPOC randomised controlled trial. Lancet Oncol. 2014;15(6):601–11.
136. Kemeny N, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med. 1999;341(27):2039–48.
137. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. N Engl J Med. 2005;352(7):734–5.
138. Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized

trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol. 2006;24(9):1395–403.
139. Kemeny N, Gonen M, Sullivan D, Schwartz L, Benedetti F, Saltz L, et al. Phase I study of hepatic arterial infusion of floxuridine and dexamethasone with systemic irinotecan for unresectable hepatic metastases from colorectal cancer. J Clin Oncol. 2001;19(10):2687–95.
140. Kemeny N, Jarnagin W, Gonen M, Stockman J, Blumgart L, Sperber D, et al. Phase I/II study of hepatic arterial therapy with floxuridine and dexamethasone in combination with intravenous irinotecan as adjuvant treatment after resection of hepatic metastases from colorectal cancer. J Clin Oncol. 2003;21(17):3303–9.
141. Onaitis MW, Petersen RP, Haney JC, Saltz L, Park B, Flores R, et al. Prognostic factors for recurrence after pulmonary resection of colorectal cancer metastases. Ann Thorac Surg. 2009;87(6):1684–8.
142. Saito Y, Omiya H, Kohno K, Kobayashi T, Itoi K, Teramachi M, et al. Pulmonary metastasectomy for 165 patients with colorectal carcinoma: a prognostic assessment. J Thorac Cardiovasc Surg. 2002;124(5):1007–13.
143. Hawkes EA, Ladas G, Cunningham D, Nicholson AG, Wassilew K, Barbachano Y, et al. Peri-operative chemotherapy in the management of resectable colorectal cancer pulmonary metastases. BMC Cancer. 2012;12:326.
144. Park HS, Jung M, Shin SJ, Heo SJ, Kim CG, Lee MG, et al. Benefit of adjuvant chemotherapy after curative resection of lung metastasis in colorectal cancer. Ann Surg Oncol. 2016;23(3):928–35.

Metastatic Colorectal Cancer

8

Mohamed E. Salem, Benjamin A. Weinberg, Feras J. Abdul Khalek, Jasmin R. Desai, Eiran A. Warner, Marion L. Hartley, and John L. Marshall

Epidemiology

Globally, colorectal cancer (CRC) represents the third most common cancer and the fourth leading cause of cancer-related deaths [1].

In the United States, an estimated 140,250 people will be diagnosed with CRC, and 50,630 will die from this disease in 2018, making CRC the second leading cause of cancer-related deaths this year [2]. An approximate 26,898 patients—20% of the total diagnosed [3]—will have metastatic disease at time of diagnosis, and, although survival time of these patients has been improved over the last few years, it is a dire but accurate assumption that only 3497 of these 26,898 patients will be alive 5 years after their diagnosis [4].

First-Line Therapy

For decades, the mainstay of treatment for metastatic colorectal cancer (mCRC) has been chemotherapy; however, comprehensive therapeutic management of mCRC should also include novel agents such as biological and immune therapies, surgery, interventional radiology, and radiation oncology. The optimal choice of therapy for first-line treatment of patients with mCRC is based on individual patient and tumor characteristics including molecular makeup. The current standard first-line treatment for inoperable mCRC is combination chemotherapy. The typical chemotherapy backbone used in mCRC treatment regimens today includes a fluoropyrimidine (either 5-fluorouracil [5-FU]/leucovorin [folinic acid] or capecitabine) with added oxaliplatin (FOLFOX, folinic acid, 5-FU, and oxaliplatin; XELOX, capecitabine and oxaliplatin), irinotecan (FOLFIRI, folinic acid, 5-FU, and irinotecan), or both (FOLFOXIRI, folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan) (Fig. 8.1) [5–19].

Patient Characteristics

First-line treatment regimens must be carefully selected based on each individual patient's clinical status and not chosen using a one-size-fits-all approach. A patient's age, performance status, and comorbidities must be taken into account in order to assess properly his or her ability to tolerate therapy. In addition, on initial diagnosis of metastatic disease, a thorough knowledge of the patient's prior CRC treatments (if applicable), treatment-related toxicities, and time since adjuvant chemotherapy is vital when it comes to

M. E. Salem
Department of Oncology, Levine Cancer Institute-Concord, Concord, NC, USA

B. A. Weinberg
Division of Hematology and Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA

F. J. Abdul Khalek
Department of Hematology and Medical Oncology, Peninsula Regional Medical Center, Salisbury, MD, USA

J. R. Desai
Department of Hematology and Oncology, Florida Cancer Specialists, Orlando, FL, USA

E. A. Warner
Department of Hematology/Oncology, Henry Ford Health System, Jackson, MI, USA

M. L. Hartley
Department of Medical Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA

J. L. Marshall (✉)
The Ruesch Center for the Cure of GI Cancers, Department of Hematology and Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA
e-mail: marshalj@georgetown.edu

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_8

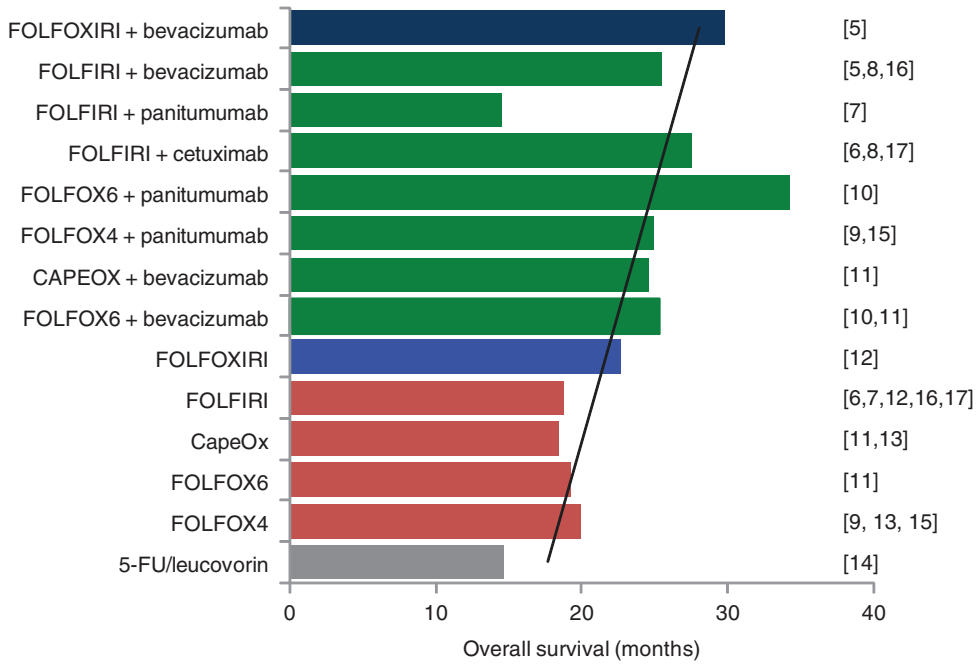


Fig. 8.1 Overall survival of patients with mCRC according to first-line treatment choice. All comparisons of chemotherapy + anti-EGFR antibodies (cetuximab or panitumumab) were for *RAS* or *KRAS* wild-type (WT) patients only. The trend line indicates improvement in patient overall survival as research has guided evolution from treatment with a fluoropyrimidine (5-FU/leucovorin) alone to a fluoropyrimidine plus oxaliplatin and/or irinotecan, to the further addition of biological agents. 5-FU 5-fluorouracil, FOLFIRI 5-FU/leucovorin/irinotecan, FOLFOX 5-FU/leucovorin/oxaliplatin, FOLFOXIRI 5-FU/leucovorin/oxaliplatin/irinotecan [5–17]

selecting the best frontline mCRC treatment. For example, if a patient develops metastatic disease while on adjuvant chemotherapy, or shortly thereafter, this suggests that their tumor is resistant to that particular chemotherapy and necessitates switching treatment. However, if a patient develops metastatic disease after completion of initial therapy, especially if longer than 6 months, then repeat use of the same agents is an option, known as "recycling."

Tumor Characteristics

RAS Mutations

Tumor-specific characteristics further dictate the selection of the most viable treatment options, and tumor profiling is essential. It was originally found that mutations in the *KRAS* gene (within codons 12 and 13 of exon 2) confer resistance to epidermal growth factor receptor (EGFR)-directed therapies such as cetuximab and panitumumab due to constitutive activation of *KRAS* and increased signaling through downstream pathways that bypass EGFR [20, 21]. More recently, it was found that the existence of extended *RAS* mutations (outside codons 12 and 13 of exon 2) further confers EGFR inhibitor resistance and, thus, an extended *RAS* mutation panel should be run on all patients with mCRC—*KRAS* and *NRAS* exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146) [22, 23].

BRAF Mutations

BRAF mutation testing should also be considered prior to instituting EGFR-directed therapy because there is evidence that patients with the *BRAF* V600E and other *BRAF* mutations (seen in approximately 10% of mCRCs) do not respond effectively to cetuximab or panitumumab due to downstream activation of the MEK-ERK pathway [24]. Possibly, this resistance could be bypassed using a BRAF inhibitor such as vemurafenib, which is currently approved by the US Food and Drug Administration (FDA) [25] for the treatment of metastatic *BRAF* V600E mutant melanoma but is still investigative for mCRC [26].

It is now understood that the presence of a *BRAF* mutation in mCRC confers a worse prognosis overall, and if a patient's metastatic colorectal tumor harbors such a mutation, a FOLFOXIRI chemotherapy regimen is recommended, pending further research [5].

Microsatellite Instability

The microsatellite stability status of CRCs has become important in the metastatic setting in addition to its biological significance in patients with localized colorectal cancer. Tumors with high microsatellite instability (MSI-high) have impaired DNA mismatch repair mechanisms and accumulate hundreds to thousands of somatic mutations. Due to this large mutational burden, these MSI-high colorectal tumors are sensitive to immune checkpoint inhibition using pembrolizumab and nivolumab, antibodies directed against pro-

grammed death 1 (anti-PD-1) [27, 28] (see "Novel Therapies" section for more information on immune checkpoint inhibition). The effectiveness of pembrolizumab compared with an investigator's choice of one of six possible standard chemotherapy regimens (mFOLFOX6, FOLFIRI, mFOLFOX6 plus bevacizumab, mFOLFOX6 plus cetuximab, FOLFIRI plus bevacizumab, or FOLFIRI plus cetuximab) is currently being assessed in the first-line setting in an international, multicenter, phase III trial (NCT02563002).

Gene Mutation Testing

As specific genetic alterations are discovered that have impact on treatment efficacy, as well as acting as biomarkers to guide treatment selection, first-line genetic sequencing of CRC will likely become commonplace. In addition to *RAS* and *BRAF* mutations, recent studies have discovered other mutations in the RAS pathway (*MAP2K1*), PI3K pathway (*PTEN* and *PIK3CA*), and TK receptor pathways (*ERBB2*, *MET*, *EGFR*, *FGFR1*, and *PDFGRA*) that confer cetuximab resistance [29]. On the other hand, *IRS2* mutations and *EGFR* amplification have been discovered that may cause cetuximab sensitivity [29]. Thus, along with the recommended extended *RAS* and *BRAF* mutation testing [30], full next-generation sequencing and MSI testing of patient colorectal tumors may soon become part of the standard of care.

Beyond gene mutation testing, it is important to define a patient's disease burden, symptomatic disease, and potential for complete tumor resectability prior to selecting initial treatment. In essence, if there is already a significant metastatic disease burden in vital organs such as the liver or lungs, a more aggressive upfront chemotherapy regimen should be considered to improve symptoms and protect organ function. In addition, if there is potential to completely resect the primary tumor and any metastases, leaving the patient with no evidence of disease (NED), this should be considered, taking all potential risks into account.

Most recently, tumor sidedness (whether the primary tumor originates from the left or right side of the colon) has emerged as an important prognostic and predictive biomarker. Patients with left-sided mCRCs (arising from the splenic flexure to the rectum) have a better overall survival and response to the anti-EGFR monoclonal antibody cetuximab than patients with metastatic right-sided CRCs (arising from the cecum to the hepatic flexure, with the transverse colon often excluded from analysis) [31–34]. The reason behind this discrepancy is not clear. There is not a dichotomous split of tumor mutational profiles between the left and right sides of the colon; rather, there is a continuum of molecular alterations that varies throughout the colon [35]. Nevertheless, the location of the primary CRC tumor plays a vital role in treatment decision-making for patients with mCRC because patients with left-sided tumors derive considerable benefit from anti-EGFR therapies, whereas those with right-sided tumors derive greater benefit from anti-vascular endothelial growth factor (VEGF) therapies [31–34].

Chemotherapy Options

FOLFOX

Studies of FOLFOX in the frontline treatment of mCRC indicate that this chemotherapy regimen provides antitumor activity and progression-free survival (PFS) benefit to some patients. In 1999, Andre et al. [36] carried out a multicenter phase II study of high-dose leucovorin, infusional 5-FU, and oxaliplatin in patients with mCRC that was resistant to leucovorin and 5-FU alone. The investigators concluded that the addition of oxaliplatin to a 5-FU/leucovorin regimen led to an "enhanced antitumor response." Subsequently, the same team, led by Aimery de Gramont [14], was the first to demonstrate that the addition of oxaliplatin to infusional 5-FU and leucovorin in the first-line setting improves the PFS of patients with mCRC. Thus, patients with untreated mCRC ($n = 422$) were randomized 1:1 to receive 5-FU plus leucovorin (leucovorin, 200 mg/m^2 intravenous [IV] over 2 hours on day 1, followed by 5-FU bolus, 400 mg/m^2 IV on day 1, and 5-FU infusion, 600 mg/m^2 on days 1 and 2 every 14 days) or 5-FU plus leucovorin in combination with oxaliplatin (the same 5-FU/leucovorin regimen plus oxaliplatin, 85 mg/m^2 IV over 2 hours on day 1). Patients in the 5-FU/leucovorin plus oxaliplatin arm had a statistically significant improvement in mPFS (9.0 vs. 6.2 months, $p = 0.0003$), although improvement in median overall survival (mOS) was not statistically significant (16.2 vs. 14.7 months, $p = 0.12$). The combination was well tolerated, and higher rates of grades 3–4 neutropenia (41.7% vs. 5.3%), diarrhea (11.9% vs. 5.3%), and neurotoxicity (18.2% vs. 0%) did not appear to translate into a worse quality of life (QOL) overall.

The "de Gramont regimen" was further modified in a subsequent dose escalation and pharmacokinetic study, leading to the now well-known FOLFOX regimen (leucovorin, 350 mg [flat-dose] IV over 2 hours; oxaliplatin, 85 mg/m^2 IV over 2 hours [concurrently with leucovorin]; bolus 5-FU 400 mg/m^2 IV; and 5-FU, 2400 mg/m^2 IV infusion over 46 hours on day 1 every 14 days) [37]. This regimen was shown to be pharmacokinetically equivalent to de Gramont's originally tested first-line regimen and was less cumbersome for patients due to the use of an ambulatory 46-hour 5-FU infusion.

Therefore, FOLFOX is an effective chemotherapy regimen for frontline mCRC, but the fact that oxaliplatin did not significantly improve mOS meant that further research efforts were necessary. In the late 2000s, the addition of biologics to 5-FU/oxaliplatin regimens began to yield positive results.

FOLFOX Combined with VEGF Inhibitors

In the TREE (Three Regimens of Eloxatin Evaluation) trial [11], Hochster et al. aimed to study the first-line treatment of patients with mCRC with oxaliplatin-fluoropyrimidine regimens plus the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab. Initially, the TREE-1 portion of the trial studied the effectiveness of three different chemotherapy regimens alone (without the addition of biologics). This trial randomized 150 patients with mCRC or recurrent CRC 1:1:1 to receive first-line treatment with mFOLFOX6 (Table 8.1 [9–11, 37–42]), bFOL (oxaliplatin, 85 mg/m^2 IV on days 1 and 15, plus leucovorin, 20 mg/m^2 IV over 10–20 minutes, followed by 5-FU, 500 mg/m^2 IV bolus on days 1, 8, and 15 every 4 weeks), or CapeOx (oxaliplatin, 130 mg/m^2 IV on day 1, plus capecitabine, 1000 mg/m^2 PO BID on days 1–15, every 3 weeks). In the TREE-2 portion of the trial (recruiting an additional 223 patients), bevacizumab was added to these regimens at doses of 5 mg/kg IV every 2 weeks (FOLFOX and bFOL) or 7.5 mg/kg IV every 3 weeks (CapeOx; capecitabine was also reduced to 850 mg/m^2 BID). The addition of bevacizumab had no major impact on the toxicity of mFOLFOX6, bFOL, and CapeOx regimens. Regarding patient survival, mOS following treatment of patients with mFOLFOX6, bFOL, and CapeOx regimens in the TREE-1 trial was 19.2, 17.9, and 17.2 months, respectively, which was subsequently improved in all cases following the addition of bevacizumab (TREE-2): 26.1, 20.4, and 24.6 months, respectively. Thus, the addition of bevacizumab to FOLFOX gave patients over 2 years of survival, and the efficacy of this combination was comparable to bevacizumab plus CapeOx. In summary, the mOS of patients treated under all three chemotherapy regimens (taken together, TREE-1) was 18.2 months (95% confidence interval [CI] = 14.5–21.6), which was increased to 23.7 months (95% CI = 21.3–26.8) following the addition of bevacizumab (TREE-2).

Table 8.1 FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) regimens

FOLFOX4 [38] every 14 days	Oxaliplatin 85 mg/m^2 IV over 2 hours on day 1
	Leucovorin 200 mg/m^2 IV over 2 hours on days 1–2 (administer concurrently with oxaliplatin on day 1)
	5-Fluorouracil 400 mg/m^2 IV bolus on days 1–2
	5-Fluorouracil 600 mg/m^2 IV over 22 hours on days 1–2
Modified FOLFOX6 (mFOLFOX6) [11, 37, 39] every 14 days	Oxaliplatin 85 mg/m^2 IV over 2 hours on day 1
	Leucovorin 400 mg/m^2 IV over 2 hours on day 1 (administer concurrently with oxaliplatin)
	5-Fluorouracil 400 mg/m^2 IV bolus on day 1
	5-Fluorouracil 2400 mg/m^2 IV over 46 hours on day 1
+ bevacizumab [10, 11] every 14 days	Bevacizumab 5 mg/kg IV (over 60 minutes) on day 1 (if well tolerated can give subsequent infusions over 10 minutes) [40]
+ cetuximab [38, 41] every 14 days	Cetuximab 400 mg/m^2 IV over 120 minutes on days 1 and 8 (loading dose, subsequent doses 250 mg/m^2 over 60 minutes on days 1 and 8) [41]
	Or
	Cetuximab 500 mg/m^2 IV on day 1 (loading dose over 120 minutes, subsequent doses over 60 minutes) [42]
+ panitumumab [9, 10] every 14 days	Panitumumab 6 mg/kg IV over 1 hour on day 1

IV Intravenous

Bevacizumab was FDA approved for the first-line treatment of patients with mCRC in 2004, following its proven efficacy in combination with standard chemotherapy as described earlier and discussed later in the IFL (irinotecan, bolus fluorouracil, and leucovorin) section of this chapter.

FOLFOX Combined with EGFR Inhibitors

Other studies evaluated the first-line treatment of patients with mCRC with FOLFOX plus the anti-EGFR monoclonal antibodies cetuximab and panitumumab. Thus, in the 2008 phase II OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer) trial, Bokemeyer et al. randomized 344 patients with EGFR-expressing untreated mCRC 1:1 to receive FOLFOX4 alone (Table 8.1) or FOLFOX4 plus cetuximab (400 mg/m^2 IV on day 1 and then 250 mg/m^2 IV every week thereafter) [38]. On initial full population data analysis, there appeared to be no significant difference in mPFS following the addition of cetuximab to chemotherapy (7.2 months in both arms, $p = 0.617$). However, on analysis of *KRAS* wild-type (WT) patients only ($n = 134$), mPFS was significantly longer in patients receiving FOLFOX4 plus cetuximab compared with FOLFOX4 alone (7.7 vs. 7.2 months, $p = 0.016$). Moreover, in patients with *KRAS*-mutated tumors ($n = 99$), mPFS was actually worse in the cetuximab arm (5.5 vs. 8.6 months, $p = 0.019$). Therefore, it was concluded that cetuximab plus FOLFOX is a first-line treatment option for patients with *KRAS* WT and extended *RAS* WT tumors only.

In the 2010 phase III, first-line treatment PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) study [9], carried out by Douillard et al. [9], patients who had not received any prior chemotherapy for mCRC were randomized 1:1 to receive FOLFOX4 plus panitumumab or FOLFOX4 alone. *KRAS* results were available for 93% of the 1183 patient recruits, and in the *KRAS* WT patients, FOLFOX4 plus panitumumab significantly improved PFS (the primary endpoint) compared with FOLFOX4 alone (9.6 vs. 8.0 months, $p = 0.02$). An increase in mOS was also observed for the panitumumab-treated patients, although this was not shown to be significant (23.9 vs. 19.7 months, $p = 0.072$). As seen for cetuximab in the Bokemeyer trial, mPFS in patients with *KRAS*-mutated

tumors was actually worsened by the addition of panitumumab to FOLFOX4 (7.3 months [FOLFOX4 + panitumumab] vs. 8.8 months [FOLFOX4 alone], $p = 0.02$), as was the pattern for mOS (15.5 vs. 19.3 months, $p = 0.068$[NS]). Results from this study emphasized the importance of *KRAS* testing in patients with mCRC and again demonstrated the effectiveness of EGFR inhibitors in the treatment of KRAS WT patients only.

Douillard et al. [15] later reported results from a prospective-retrospective analysis of subjects from the PRIME study. Of the 93% of patients who underwent tumor testing for *KRAS* exon 2 ($n = 1096$), 656 were *KRAS* WT and 440 were *KRAS* mutant. The investigators went on further to analyze for mutations in *KRAS* exons 3 and 4; *NRAS* exons 2, 3, and 4; and *BRAF* exon 15. Of the 1060 patients, 512 (48%) were found to have extended RAS WT tumors (no *KRAS* or *NRAS* mutations in exons 2, 3, or 4). The other 548 (52%) had mutated *RAS* tumors (any *KRAS* or *NRAS* mutations in exon 2, 3, or 4).

Among the 512 patients who had no *RAS* mutations, mPFS was 10.1 months following treatment with FOLFOX4 plus panitumumab but only 7.9 months with FOLFOX4 alone ($p = 0.004$). mOS was 26.0 months and 20.2 months, respectively ($p = 0.04$). One hundred eight patients (17%) who were originally categorized as KRAS WT had extended *RAS* mutations, and the existence of these mutations was associated with shorter PFS and OS following FOLFOX4 plus panitumumab treatment (consistent with results found for patients with *KRAS* exon 2 mutations in the original PRIME study [9]). *BRAF* mutations were also related with a negative prognosis.

In the phase II PEAK (Panitumumab Efficacy in Combination With mFOLFOX6 Against Bevacizumab Plus mFOLFOX6 in mCRC Subjects With Wild-Type KRAS Tumors) trial, Schwartzberg et al. prospectively randomized 285 patients who had not yet been treated for their *KRAS* exon 2 WT mCRC to mFOLFOX6 plus panitumumab or mFOLFOX6 plus bevacizumab (Table 8.1) [10]. Median OS was significantly longer for the panitumumab-treated patients (34.2 months) than for the bevacizumab-treated patients (24.3 months; $p = 0.009$).

From the studies presented here, it can be concluded that FOLFOX plus cetuximab and FOLFOX plus panitumumab are appropriate first-line treatment options for patients with *RAS* WT mCRC, and the addition of biologics to FOLFOX provides better survival than FOLFOX alone. However, any EGFR inhibitor combined with chemotherapy should be avoided in patients with *RAS* mutant mCRC. These findings emphasize the importance of extended *RAS* testing.

In early 2014, the FDA approved the use of panitumumab in combination with FOLFOX for the first-line treatment of patients with *KRAS* (exon 2 in codons 12 or 13) WT mCRC. This approval was based on results from the PRIME and ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With KRAS Wild-Type Metastatic Colorectal Cancer) trials (discussed in "Third-Line Therapy" section of this chapter).

XELOX

Capecitabine is an oral pro-drug that is enzymatically converted to 5-FU once ingested [43]. Its use avoids long IV infusions, which is desirable for many individuals. As described previously by both Hochster et al. [11] and Cassidy et al. [13], the addition of oxaliplatin to capecitabine (XELOX; also called CapeOx) yields more or less equivalent patient survival results to FOLFOX, and this survival is similarly increased by the addition of bevacizumab to the mix [11].

XELOX Combined with Bevacizumab

Cassidy et al. [13] conducted a phase III trial that initially randomized 634 patients with untreated mCRC 1:1 to receive XELOX (Table 8.2 [11, 13, 44]) or FOLFOX4 (Table 8.1). The investigators then amended the study protocol to allow randomization of an additional 1400 patients using a 2 × 2 factorial design to receive XELOX or FOLFOX4 along with bevacizumab or placebo. The mPFS was longer in the chemotherapy plus bevacizumab arms than in the chemotherapy plus placebo arms (9.4 vs. 8.0 months, $p = 0.0023$), although any improvement in mOS was not statistically significant (21.3 vs. 19.9 months, $p = 0.0769$). When comparing all XELOX with FOLFOX4 treatment arms, the mPFS and mOS were non-inferior [13]. Thus, XELOX was shown to be equivalent to FOLFOX4, and the addition of bevacizumab further improved mPFS compared with placebo (XELOX or FOLFOX4 alone).

IFL

Saltz et al. demonstrated that adding irinotecan to bolus fluorouracil and leucovorin (IFL) significantly prolonged mPFS (7.0 vs. 4.3 months, $p = 0.004$) and mOS (14.8 vs. 12.6 months, $p = 0.04$) in patients with previously untreated mCRC [45]. Hurwitz et al. then demonstrated that IFL plus bevacizumab (5 mg/kg IV every 14 days) was superior to IFL plus placebo in terms of mPFS (10.6 vs. 6.2 months, $p < 0.001$) and mOS (20.3 vs. 15.6 months, $p < 0.001$) [46]. This finding led to the FDA approval of bevacizumab as a first-line treatment for patients with mCRC.

Table 8.2 XELOX (capecitabine and oxaliplatin) regimens

XELOX [11, 13, 44] every 21 days	Oxaliplatin 130 mg/m^2 IV over 2 hours on day 1
	Capecitabine 850–1000 mg/m^2 PO twice daily on days 1–14
+ bevacizumab [11, 13] every 21 days	Bevacizumab 7.5 mg/kg IV over 30–90 minutes on day 1

FOLFIRI Combined with VEGF or EGFR Inhibitors

Fuchs et al. [16] studied the best way to integrate irinotecan into treatment regimens for patients with mCRC and sought to investigate whether the addition of biological agents to irinotecan regimens in the first line improved patient survival. In this phase III BICC-C (Bevacizumab plus Irinotecan in Colorectal Cancer) trial, 430 patients with untreated mCRC were first randomized 1:1:1 to receive FOLFIRI, mIFL (modified irinotecan, 5-FU, and leucovorin), or CapeIRI (capecitabine and irinotecan) (Table 8.3 [5–8, 16, 17, 39–42, 47, 48]). Patient mPFS was shown to be significantly longer following treatment with FOLFIRI than with mIFL (7.6 vs. 5.9 months, $p = 0.004$) or CapeIRI (7.6 vs. 5.8 months, $p = 0.015$), although improvements observed in mOS were not statistically significant (23.1 vs. 17.6 months for FOLFIRI vs. mIFL [$p = 0.09$] and 23.1 vs. 18.9 months for FOLFIRI vs. CapeIRI [$p = 0.27$]). The researchers then randomized an additional 117 patients to FOLFIRI plus bevacizumab (5 mg/kg IV on day 1 every 14 days) or mIFL plus bevacizumab (7.5 mg/kg IV on day 1 every 21 days). FOLFIRI plus bevacizumab was seen to significantly prolong mOS compared with mIFL plus bevacizumab (28.0 vs. 19.2 months [$p = 0.037$] at an extended follow-up time of 34.4 months [49]). However, this survival benefit came with the payoff of higher rates of nausea and vomiting (10.7% vs. 5.1%), neutropenia (53.6% vs. 28.8%), febrile neutropenia (5.4% vs. 1.7%), and hypertension (12.5% vs. 1.7%) [16].

Table 8.3 5-Fluorouracil (5-FU)/irinotecan regimens

FOLFIRI [39] every 14 days	Irinotecan 180 mg/m^2 IV over 90 minutes on day 1 (administered concurrently with leucovorin)
	Leucovorin 400 mg/m^2 IV over 2 hours on day 1
	5-Fluorouracil 400 mg/m^2 IV bolus on day 1
	5-Fluorouracil 2400 mg/m^2 IV over 46 hours on day 1
+ bevacizumab [5, 8, 16] every 14 days	Bevacizumab 5 mg/kg IV over 90 minutes on day 1 (if well tolerated can give subsequent infusions over 10 minutes) [40]
+ cetuximab [6, 8, 17] every 14 days	Cetuximab 400 mg/m^2 IV over 120 minutes on days 1 and 8 (loading dose, subsequent doses 250 mg/m^2 over 60 minutes on days 1 and 8) [41]
	Or
	Cetuximab 500 mg/m^2 IV on day 1 (loading dose over 120 minutes, subsequent doses over 60 minutes) [42]
+ panitumumab [7, 47] every 14 days	Panitumumab 6 mg/kg IV over 60 minutes on day 1
CapeIRI [16, 48] every 21 days	Irinotecan 250 mg/m^2 IV over 90 minutes on day 1
	Capecitabine 1000 mg/m^2 PO BID on days 1–14
mIFL [16] every 21 days	Irinotecan 125 mg/m^2 IV over 90 minutes on days 1 and 8
	Leucovorin 20 mg/m^2 IV bolus on days 1 and 8
	5-FU 500 mg/m^2 IV bolus on days 1 and 8

FOLFIRI Folinic acid, 5-FU, and irinotecan, *IV* intravenous, *CapeIRI* capecitabine and irinotecan, *mIFL* modified irinotecan, 5-FU, and leucovorin

In the phase III CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) trial, Van Cutsem et al. [6] randomized 1198 patients with untreated EGFR-expressing mCRC 1:1 to receive FOLFIRI alone or FOLFIRI plus cetuximab (400 mg/m^2 IV over 120 minutes on day 1, followed by 250 mg/m^2 IV weekly). Only 540 patients had pretreatment tumor biopsy samples that were suitable for *KRAS* mutation analysis, and 348 of these patients had tumors that were *KRAS* WT, whereas 192 patients had *KRAS*-mutated tumors. When assessed according to treatment group, 66.9% of patients in the FOLFIRI arm and 62.1% of patients in the FOLFIRI plus cetuximab arm had *KRAS* WT tumors. Thus groups were equally matched for analysis. Taking these *KRAS* WT patients only, mPFS was improved in the cetuximab arm (9.9 vs. 8.7 months; hazard ratio [HR] = 0.68, 95% CI = 0.50–0.94), but the difference in mOS (24.9 vs. 21.0 months) was not significantly different between the two treatment groups. In patients with *KRAS*-mutated tumors treated with FOLFIRI plus cetuximab, mPFS and mOS appeared to be lower than with FOLFIRI alone (mPFS, 7.6 vs. 8.1 months; mOS, 17.5 vs. 17.7 months). In patients with *KRAS* WT tumors, FOLFIRI with and without cetuximab led to tumor response rates (RRs) of 59.3% (with cetuximab) and 43.2% (without cetuximab), whereas patients with *KRAS*-mutated tumors had RRs of 36.2% (FOLFIRI plus cetuximab) vs. 40.2% (FOLFIRI alone). This work provided further evidence for the impact of *KRAS* mutational status on EGFR inhibitor efficacy (but not FOLFIRI alone).

An updated analysis of a much larger group of patients with *KRAS* WT mCRC ($n = 666$) demonstrated statistically significant improvements in both mPFS (9.9 vs. 8.4 months, $p = 0.001$) and mOS (23.5 vs. 20.0 months, $p = 0.009$), favoring the cetuximab arm [17]. Cetuximab was associated with a slightly higher incidence of neutropenia (28.2% vs. 24.9%) and higher incidences of skin reactions (19.5% vs. 0.2%) and infusion-related reactions (2.3% vs. 0%). Therefore, all things considered, FOLFIRI plus cetuximab is a valid first-line treatment option for *KRAS* WT mCRC.

In 2012, following CRYSTAL study results, as well as those from the OPUS and CA225025 trials (discussed in "Third-Line Therapy" section), cetuximab was FDA approved for use in combination with FOLFIRI for first-line treatment of patients with *KRAS* WT, EGFR-expressing mCRC.

In the FIRE-3 (Multicenter Randomized Trial Evaluating FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First-Line Treatment of Metastatic Colorectal Cancer) trial [8], Heinemann et al. set out to determine whether

cetuximab or bevacizumab is the better biologic to add to a FOLFIRI regimen in the frontline treatment of patients with KRAS WT tumors. This research team randomized 592 patients with untreated *KRAS* WT mCRC 1:1 to receive FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab [8]. Median PFS was found to be similar between the two arms (10.0 months in the cetuximab arm vs. 10.3 months in the bevacizumab arm, $p = 0.55$), but mOS was improved with cetuximab (28.7 vs. 25.0 months, $p = 0.017$). To determine if response varied according to extended *RAS* WT vs. *KRAS* (exon 2) WT status, response in patients with an extended *RAS* WT tumor profile was retrospectively analyzed. Thus, mPFS was still similar (10.4 months in the cetuximab arm vs. 10.2 months in the bevacizumab arm), but mOS was further improved to 33.1 months in the cetuximab arm compared with 25.6 months in the bevacizumab arm ($p = 0.011$). These findings support the FDA approval of cetuximab in this setting and suggest that FOLFIRI plus cetuximab is superior to FOLFIRI plus bevacizumab in all patients with *KRAS* WT mCRC and especially in patients with extended *RAS* WT tumors.

The phase III Cancer and Leukemia Group B/Southwest Oncology Group (CALBG/SWOG) 80,405 trial [50] enrolled 2334 patients with untreated *KRAS* WT mCRC to initially receive FOLFIRI or mFOLFOX6 (at the discretion of the physician and patient). Seventy-three percent of patients received mFOLFOX6, and the rest received FOLFIRI before being randomized 1:1 to receive cetuximab (400 mg/m^2 IV over 120 minutes and then 250 mg/m^2 IV over 60 minutes weekly) or bevacizumab (5 mg/kg IV over 90 minutes every 2 weeks) in combination with their chemotherapy. Neither mPFS nor mOS were significantly different between chemotherapy plus bevacizumab and chemotherapy plus cetuximab treatment arms (mPFS, 10.84 vs. 10.45 months; mOS, 29.04 vs. 29.93 months [$p = 0.34$]). The difference between this study and the FIRE-3 trial is the CALBG/SWOG study investigators' incorporation of FOLFOX into their statistical analysis.

Although a phase III trial of panitumumab plus FOLFIRI in the second-line mCRC setting hinted that adding panitumumab to FOLFIRI resulted in a mOS benefit for patients with *KRAS* WT tumors [7, 47], no large definitive trials of panitumumab plus FOLFIRI have been performed in the first-line setting. FOLFIRI plus panitumumab remains a first-line treatment option in *KRAS* and *NRAS* WT mCRC patients according to National Comprehensive Cancer Network (NCCN) guidelines [30]; however, before committing to the use of panitumumab in this role, it would be encouraging to see some efficacy-supporting data.

FOLFOXIRI

With the hope of achieving greater efficacy in the treatment of patients with mCRC, the combination of 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI; Table 8.4 [5, 12, 51]) was evaluated by Falcone et al. [12], comparing this full arsenal with FOLFIRI alone (irinotecan, 180 mg/m^2 IV over 60 minutes on day 1, plus leucovorin, 100 mg/m^2 IV over 2 hours, followed by 5-FU, IV bolus 400 mg/m^2, then 5-FU, 600 mg/m^2 IV infusion over 22 hours on days 1–2, every 14 days). In this phase III trial, 244 patients with untreated mCRC were randomized 1:1 to receive FOLFOXIRI or FOLFIRI. Median PFS was significantly longer in the FOLFOXIRI arm (9.8 vs. 6.9 months, $p = 0.0006$), as was mOS (22.6 vs. 16.7 months, $p = 0.032$). Compared with FOLFIRI, FOLFOXIRI treatment of patients was associated with a higher incidence of grades 2–3 neuropathy (19% vs. 0%, $p < 0.001$) and grades 3–4 neutropenia (50% vs. 28%, $p < 0.001$), although febrile neutropenia was not significantly different (3% vs. 5%, $p = 0.75$).

FOLFOXIRI Combined with Bevacizumab

The larger, phase III TRIBE study randomized 508 patients with untreated mCRC 1:1 to receive FOLFOXIRI plus bevacizumab (Table 8.4) or FOLFIRI plus bevacizumab (as described in Table 8.3, except leucovorin was dosed at 200 mg/m^2 IV over 120 minutes) [5]. Treatment consisted of 12 cycles of therapy, followed by maintenance 5-FU, leucovorin, and bevacizumab until intolerability or disease progression. In the intent-to-treat population, FOLFOXIRI plus bevacizumab yielded significantly longer mPFS (12.3 vs. 9.7 months, $p = 0.006$) and mOS (29.8 vs. 25.8 months, $p = 0.03$) than FOLFIRI plus bevacizumab.

The authors updated their initial study to include analysis of mOS according to patient tumor *RAS* and *BRAF* molecular subtype. Thus, mOS was 37.1 months (29.7–42.7) in the *RAS* and *BRAF* WT subgroup, 25.6 months (22.4–28.6) in the *RAS* mutant subgroup (HR = 1.49, 95% CI = 1.11–1.99), and 13.4 months (8.2–24.1) in the *BRAF* mutant subgroup (HR = 2.79, 95% CI = 1.75–4.46), $p < 0.0001$ by likelihood ratio test. However, regarding the predictive effect of *RAS* and *BRAF* status, treatment effect on mOS was not significantly different across all molecular subgroups (p-interaction = 0.52).

Table 8.4 FOLFOXIRI

FOLFOXIRI [12] every 14 days	Irinotecan 165 mg/m^2 IV over 60 minutes
	Oxaliplatin 85 mg/m^2 IV over 120 minutes on day 1
	Leucovorin 200 mg/m^2 IV over 120 minutes on day 1 (administer concurrently with oxaliplatin)
	5-Fluorouracil 3200 mg/m^2 IV over 48 hours on day 1
+ bevacizumab [5, 51] every 14 days	Bevacizumab 5 mg/kg IV over 30 minutes on day 1

FOLFOXIRI 5-Fluorouracil, leucovorin, oxaliplatin, and irinotecan

Nevertheless, it can be concluded from all available literature that *BRAF* mutational status gives patients a generally bad prognosis for chemotherapy treatment, and until an alternative comes to light, one school of thought embraces pulling out all the stops and treating patients with *BRAF* mutant mCRC with a full FOLFOXIRI regimen.

Chemotherapy Combined with VEGF and EGFR Inhibitors

Combining both anti-EGFR and anti-VEGF agents with chemotherapy in the first-line treatment of patients with mCRC resulted in adverse outcomes or at least was not helpful in two large randomized phase III trials [18, 19]. The Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study [18] reported excess toxicity and higher death rates from the combination of panitumumab, bevacizumab, and chemotherapy (fluorouracil, leucovorin, and oxaliplatin- or irinotecan-based), with a worsening PFS over all (10.0 months compared with 11.4 months for patients treated with chemotherapy plus bevacizumab only). "A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG)" [19], was carried out in patients with untreated mCRC. The primary endpoint of this trial was an improvement in PFS following double antibody use. Again, in this study, adding cetuximab worsened PFS for the whole population. Subset analysis demonstrated that there was no effect in patients with *KRAS* WT tumors, but a marked detrimental effect in patients with *KRAS*-mutated tumors. Ongoing studies including a SWOG trial are re-examining the combination of VEGF and EGFR inhibitors in the appropriately enriched patient population (all RAS WT).

Surgical Options

Hepatic Metastasectomy

Given that 23–51% of patients with mCRC have a resectable primary tumor, which presents with synchronous liver metastases [52], the decision as to whether to simultaneously resect liver lesions at the time of resection of the primary CRC or perform a "staged" resection, thus delaying the hepatic metastasectomy, has been frequently debated. Partial hepatectomy for patients with resectable metastases to the liver alone has long been considered the standard of care [53]. Reddy et al. performed a multi-institutional retrospective analysis of 135 patients who underwent simultaneous resection and 475 who had staged surgeries [54]. Patients who had a simultaneous resection along with minor hepatectomy (defined as removal of fewer than three hepatic segments) were compared with those who had staged resection with minor hepatectomy. The two groups had similar mortality (1.0% vs. 0.5%, $p > 0.05$) and severe morbidity (14.1% vs. 12.5%, $p > 0.05$). Outcomes were worse following any major hepatectomy, particularly when resected simultaneously with the primary tumor (HR for death = 3.4, $p = 0.008$). Thus, simultaneous resection with minor hepatectomy is safe and is the standard of care for patients with resectable mCRC.

The question was posed as to whether neoadjuvant chemotherapy should be offered to patients with resectable liver-only metastases. The phase III European Organisation for Research and Treatment of Cancer (EORTC) 40,983 trial randomized 364 patients with mCRC and up to 4 liver metastases 1:1 to receive perioperative FOLFOX4 and surgery or surgery alone. Although there was no statistically significant difference in mOS between the two treatment groups (61.3 months for chemotherapy plus surgery vs. 54.3 months for surgery alone, $p = 0.34$), mPFS was significantly longer in the patients who received chemotherapy plus surgery (20.9 months vs. 12.5 months, $p = 0.035$) [55]. These results suggest that perioperative chemotherapy may play a positive role in the treatment of patients with resectable liver-only metastases.

Pulmonary Metastasectomy

Similarly, pulmonary metastases are common in mCRC, and pulmonary metastasectomies are widely performed. A retrospective study of 94 patients by Suzuki et al. [56] demonstrated a 5-year survival rate of 45.5% following pulmonary metastasectomy. Survival was especially prolonged in patients with preoperative carcinoembryonic antigen (CEA) levels that were defined as normal vs. elevated (57.0 vs. 30.9% at 5 years, $p = 0.038$) and in patients with primary colon vs. rectal cancer (62.4% vs. 33.8% at 5 years, $p = 0.030$). Those with solitary pulmonary metastases showed a trend toward improved 5-year survival, but this was not statistically significant (52.1% vs. 35.1% for multiple metastases, $p = 0.058$). Unfortunately, patients frequently had recurrent disease in the liver or lungs (65 out of 94 patients; 69.1%). Among 22 patients who underwent further surgical treatment after recurrence, 5-year survival after initial resection was 75.6%, compared with 12.5% in the 13 patients who received non-surgical treatment and 0% in the 4 patients who received palliative care only ($p < 0.001$ between all groups). Although pulmonary metastasectomy is an important treatment option, particularly for patients with normal preoperative CEA levels, colon primary cancers, and perhaps only one solitary lesion, these results need to be further validated in a randomized trial.

Conversion Therapy (Neoadjuvant)

Induction chemotherapy can render a patient with initially unresectable liver metastases eligible for curative resection. However, the usefulness of this practice remains under debate. In the multicenter phase II Cetuximab in Neoadjuvant

Treatment of Non-Resectable Colorectal Liver Metastases (CELIM) trial, Folprecht et al. treated 111 patients with mCRC and technically unresectable and/or ≥ 5 liver-only metastases with chemotherapy (either FOLFOX or FOLFIRI) plus cetuximab [57, 58]. Patient metastases were assessed for resectability potential every 2 months. Thirty-six patients underwent "secondary" R0 resection ($n = 36$), and their mOS (53.9 months, 95% CI = 35.9–71.9) was much better than those who did not undergo R0 resection (21.9 months; 95% CI = 17.1–26.7, $p < 0.001$). This study confirmed that, on responding to induction/conversion therapy, patients with unresectable liver metastases from primary CRC could undergo secondary resection, which allowed them to live longer than those who did not receive or respond to conversion therapy and therefore could not undergo tumor resection [57]. This study took place from 2004 until 2008, before the necessity of *RAS* testing prior to cetuximab treatment was common knowledge. A retrospective analysis of response according to *KRAS* status showed that patients who had *KRAS* WT tumors had significantly improved response and resection rates compared with patients with KRAS-mutated tumors [58].

In the TRIBE study (discussed previously), adding oxaliplatin to a FOLFIRI (plus bevacizumab) regimen did not significantly increase the R0 resection rate (12% following FOLFIRI/bevacizumab vs. 15% following FOLFOXIRI/bevacizumab, $p = 0.33$) [51]. In the phase II OLIVIA trial, Gruenberger et al. [59] randomized 80 patients with mCRC and unresectable liver-only metastases 1:1 to receive mFOLFOX6 plus bevacizumab or FOLFOXIRI plus bevacizumab. The R0 resection rate was higher with FOLFOXIRI plus bevacizumab compared with mFOLFOX6 plus bevacizumab (49% [95% CI = 33–65] vs. 23% [95% CI = 11–39]), and mPFS was longer (18.6 months [95% CI = 12.9–22.3] vs. 11.5 months [95% CI = 9.6–13.6]). There appears to be a role for FOLFOXIRI plus bevacizumab in the conversion of patients with liver-only metastases to resectable disease status.

The optimal induction regimen should be determined by the ongoing CAIRO5 study, which is treating patients with mCRC and unresectable liver-only metastases differently depending on their tumors' *RAS* mutation status. Thus, *RAS* WT patients will be treated with doublet chemotherapy (FOLFOX or FOLFIRI) and randomized to additionally receive bevacizumab or panitumumab, whereas *RAS* mutant patients will be randomized to doublet chemotherapy (FOLFOX or FOLFIRI) plus bevacizumab or triplet chemotherapy (FOLFOXIRI) plus bevacizumab (NCT02162563) [60].

Adjuvant Therapy After Metastasectomy

Portier et al. [61] showed that patients with mCRC and liver-only metastases who underwent R0 resection and adjuvant therapy with 5-FU plus leucovorin did better than those who received surgery alone (the 5-year disease-free survival rate was 33.5% following chemotherapy plus surgery vs. 26.7% following surgery alone, $p = 0.028$). Subsequently, Ychou et al. [62] randomized 306 patients with mCRC and resected liver-only metastases 1:1 to receive infusional 5-FU plus leucovorin or FOLFIRI for 12 cycles. There were no statistically significant differences between the groups with respect to either mPFS (21.6 months vs. 24.7 months, $p = 0.44$) or 3-year mOS (71.6% vs. 72.7%, $p = 0.69$). Patients in the FOLFIRI arm had higher rates of grade 3/4 neutropenia (23% vs. 7%) and diarrhea (14% vs. 7%). Therefore, although use of a 5-FU-based adjuvant regimen is superior to surgery alone, the optimal drug regimen in this setting has not been firmly established.

Liver-Directed Therapy

Hepatic Arterial Infusion

For patients treated at centers proficient in hepatic arterial infusion (HAI) therapy techniques, there is a survival benefit to HAI after resection of liver-only metastases. Kemeny et al. [63] randomized 156 patients with resected liver metastases 1:1 to receive 5-FU/leucovorin plus HAI or 5-FU/leucovorin alone. Four weeks after resection of liver metastases, patients in the HAI arm received leucovorin (200 mg/m^2 IV over 30 minutes) plus 5-FU (325 mg/m^2 IV bolus) on days 1–5 followed 2 weeks later by HAI (floxuridine 0.25 mg/kg/day, dexamethasone 20 mg, and 50,000 units of heparin daily) for another 2 weeks. Patients then had 1 week off before the next cycle of treatment (six cycles in total). Patients in the 5-FU/leucovorin-only arm (no HAI) received leucovorin (200 mg/m^2 IV) plus 5-FU (IV bolus 370 mg/m^2 IV on days 1–5) every 4 weeks for a total of six cycles. The 2-year OS rate for patients in the HAI group vs. the non-HAI group was 86% vs. 72% ($p = 0.03$). The 2-year hepatic recurrence-free survival rate was 90% in the HAI group vs. 60% in the non-HAI group ($p < 0.001$). Increased toxicities in the HAI group included higher rates of diarrhea (29% vs. 14%) and elevation in liver test values. It seems that HAI in this patient population is a viable treatment option at HAI-experienced centers.

Transarterial Radioembolization

Transarterial radioembolization (TARE) involves the insertion of radioactive isotope (e.g., yttrium-90 [Y-90]) embedded microspheres into the main hepatic artery, resulting in radioactivity levels within liver tumors of up to 5–6 times that reached within normal liver [64]. The SIRFLOX trial randomly assigned patients with untreated liver-only or liver-predominant mCRC (with lung and/or lymph node metastases) to receive mFOLFOX6 or mFOLFOX6 plus SIR-Spheres® Y-90 resin microspheres, administered during days 3–4 of the first cycle of mFOLFOX6, plus or minus bevacizumab. mPFS at any site was 10.7 months in the SIR arm vs. 10.2 months in

the chemotherapy-only arm (p = 0.43; NS), although SIR appeared to prolong liver mPFS (20.5 months vs. 12.6 months, p = 0.002) [65]. A combined analysis of the SIRFLOX and similar FOXFIRE and FOXFIRE-Global trials demonstrated no improvement in mOS with the addition of SIR therapy [66]. Thus, TARE may play a role in the later-line treatment of patients with mCRC and liver-predominant metastases as a consolidative treatment following chemotherapy. Further studies are required to better delineate the role for SIR therapy in the treatment of mCRC.

Summary

There are a multitude of treatment options for untreated mCRC. Thus, initial therapy must be chosen carefully by taking into account the unique characteristics of the patient, including disease burden and performance status, as well as the tumor's genetic signature (e.g., the tumor's *RAS* and *BRAF* mutational status) and primary tumor sidedness. In addition, the upfront use of more aggressive and toxic regimens (such as FOLFOXIRI) versus sequencing chemotherapy regimens is constantly debated. Treatment should be designed to prioritize surgery for potential R0 metastasectomies or to reduce tumors to R0 resection status. TARE is currently more frequently used than HAI in liver-predominant mCRC, although an OS benefit to TARE has yet to be reported. The frontline management of patients with mCRC necessitates the close collaboration of medical oncologists, surgeons, radiation oncologists, and interventional radiologists to guide patients through increasingly complex treatment regimens.

Maintenance Therapy and Second-Line Therapy

Maintenance therapy is usually defined as that administered to prevent the reemergence of cancer following successful first-line therapy, whereas second-line therapy is generally defined as that given to patients when first-line therapy has failed to yield the desired cancer-remission results (www.cancer.gov).

As we outlined earlier, the recommended (standard) first-line treatment for inoperable mCRC is 5-FU plus oxaliplatin and/or irinotecan (FOLFOX, FOLFIRI, or FOLFOXIRI). The VEGF inhibitor bevacizumab or EGFR inhibitors cetuximab and panitumumab may be administered along with this chemotherapy. The administration of EGFR inhibitors is, of course, dependent on the *RAS* status of any particular patient's mCRC. Although it has been known for some time that patients gain greater benefit from access to all active agents as opposed to individual "lines" of therapy, the best way to combine and sequence these agents is not well defined.

Additionally, in the majority of patients, chemotherapy treatment will be palliative and not curative. Therefore, the treatment goals are to prolong OS with the least possible side effects and maintain quality of life.

The optimal duration of initial first-line chemotherapy for unresectable disease is not well defined; thus there is an urgent need for a better-defined optimal sequence and duration of therapy. A strategy that has recently emerged is the concept of maintenance therapy, which is categorized as either continuation maintenance therapy or switch maintenance therapy. Continuation maintenance therapy involves continuation of a defined number of cycles of combination induction (first-line) therapy (usually involving a chemotherapy agent combined with a targeted agent) in the absence of disease progression, whereas switch maintenance therapy involves administration of a combined chemotherapeutic induction (first-line) regimen for a predetermined number of cycles, followed by treatment with a different agent in the absence of disease progression.

Maintenance Therapy

There are a number of good reviews on the topic of maintenance therapy in mCRC such as those by Grothey et al. [67, 68]. The use of oxaliplatin in first-line combination therapy often decreases tumor burden but also results in cumulative toxicity. If a patient with mCRC is responding well to FOLFOX or XELOX in the first-line and cumulative side effects are not an issue, the continuation of this therapy until tumor progression is considered reasonable. However, a number of other strategies have emerged that attempt to improve the clinical benefit of first-line treatment for patients with mCRC, allowing maintenance of stable disease while avoiding extreme toxicity. For example, intermittent therapy (using "stop-and-go strategies") until best response is achieved followed by a chemotherapy "holiday" has been attempted using regimens that contain oxaliplatin [69, 70]. With this approach, patients who respond to an initial oxaliplatin-based regimen discontinue treatment (have a treatment holiday) before the onset of severe neurotoxicity, usually after 3–4 months of therapy. However, a complete treatment holiday comes with the risk of tumor progression and reduced patient survival, and many believe that a better approach is to switch to "maintenance" chemotherapy involving 5-FU/leucovorin or capecitabine with or without bevacizumab before the onset of oxaliplatin-induced neuropathy. This translates into an oxaliplatin holiday as opposed to a complete chemotherapy holiday. The idea is that oxaliplatin can then be restarted at the time of cancer progression on the fluorouracil +/− bevacizumab regimen.

The OPTIMOX1 study (2006; Table 8.5 [69–80]) was carried out to determine if an oxaliplatin holiday involving administration of maintenance 5-FU only could be as effective as continuous FOLFOX while being more tolerable for patients and allowing them to continue their chemotherapy as scheduled [69]. Investigators randomized 620 patients with inoperable advanced colon cancer 1:1 to receive either FOLFOX4 (Table 8.1) administered every 2 weeks until progression (arm A) or FOLFOX7 administered every 2 weeks for 6 cycles, followed by maintenance leucovorin/5-FU therapy without oxaliplatin for 12 cycles, and then reintroduction of FOLFOX7 for another 6 cycles (arm B).

Results showed that the group with the oxaliplatin interruption (FOLFOX7 arm) had the same PFS, OS, and objective tumor RR as the group given oxaliplatin continuously (FOLFOX4 arm). As expected, grade 3–4 toxicity was reduced during the 12 off-oxaliplatin cycles. This study concluded that six cycles of FOLFOX7 gave sufficient oxaliplatin to reap its clinical benefits, although there was poor compliance to the reintroduction of oxaliplatin with frequent protocol violations: approximately 75% of patients had delayed reintroduction of oxaliplatin [69].

The OPTIMOX2 trial (2009; Table 8.5) was designed to assess the need for 5-FU maintenance treatment as opposed to just surveillance after FOLFOX induction therapy [70]. Two hundred patients were randomized to receive induction therapy with six cycles (3 months) of mFOLFOX7 followed by either maintenance leucovorin/5-FU therapy (arm 1) or a "chemotherapy-free interval (CFI)" (arm 2) until progression. Reintroduction of mFOLFOX7 was implemented upon tumor progression in both arms.

The study results showed that maintenance therapy with 5-FU is superior to a CFI. Thus, patients who received maintenance therapy with 5-FU had better PFS (8.6 months vs. 6.6 months; HR = 0.61, $p = 0.0017$) and OS (23.8 months vs. 19.5 months; HR = 0.88, $p = 0.42$).

Both OPTIMOX1 and OPTIMOX2 study results suggest that an oxaliplatin holiday, lasting at least 6 months, is an

Table 8.5 Maintenance trials in patients with mCRC

Maintenance trials	Agents used	Comments
OPTIMOX1 [69]	Continuous FOLFOX4 regimen or FOLFOX7 (oxaliplatin [130 mg/m^2] on day 1, followed by leucovorin and 46 hour IV 5-FU [2400 mg/m^2]) every 2 weeks for six cycles, followed by 12 × 2 week cycles of leucovorin/5-FU (3000 mg/m^2), followed again by FOLFOX7 (six cycles)	On FOLFOX treatment, oxaliplatin interruption resulted in the same patient PFS, OS, and RR as continuous oxaliplatin
OPTIMOX2 [70]	mFOLFOX7 (oxaliplatin [100 mg/m^2] on day 1, followed by leucovorin and 48-hour IV 5-FU [3000 mg/m^2]) for 6 × 2 week cycles, then maintenance with 5-FU/leucovorin (arm 1) or a chemotherapy-free interval (arm 2) until progression, followed by reintroduction of mFOLFOX7 (6 × 2 week cycles)	Patients who received maintenance with 5-FU had significantly better PFS and a trend toward increased OS when compared with surveillance only
GISCAD [71]	Irinotecan 180 mg/m^2 on day 1 and 5-FU 400 mg/m^2 (bolus) and 600 mg/m^2 (infusion) in continuous 2-week cycles. The maintenance arm received four of these 2-week cycles above, then 2 months of surveillance, and then reinitiation of this regimen for four more cycles	When using irinotecan and 5-FU (FOLFIRI), a chemotherapy-free interval is not inferior to continuous treatment
MACRO-TTD [72]	XELOX (oxaliplatin, 130 mg/m^2 on day 1, capecitabine 1000 mg/m^2 twice daily on days 1–14 every 3 weeks); bevacizumab (7.5 mg/kg on day 1 every 3 weeks)	Bevacizumab maintenance therapy was equivalent to bevacizumab + XELOX maintenance therapy but with less toxicity
SAKK 41/06 [73]	Bevacizumab (7.5 mg/kg on day 1 every 3 weeks)	Investigators could not confirm non-inferiority between no maintenance therapy vs. bevacizumab maintenance therapy
CAIRO-3 [74]	CAPOX-Bev (capecitabine 1000 mg/m^2 twice daily on days 1–14, oxaliplatin 130 mg/m^2 on day 1, bevacizumab 7.5 mg/kg on day 1); maintenance capecitabine (625 mg/m^2 twice daily continuously); maintenance bevacizumab (7.5 mg/kg every 3 weeks)	Maintenance treatment with bevacizumab + capecitabine was effective and does not compromise quality of life
AIO-0207 [75]	LV5-FU2 (400 mg/m^2 bolus and 2400 mg/m^2 46 hour infusion); capecitabine; maintenance bevacizumab (7.5 mg/kg every 3 weeks)	Although bevacizumab was not inferior, maintenance treatment with a fluoropyrimidine plus bevacizumab may be the preferable option
GERCOR DREAM; OPTIMOX3 [76]	mFOLFOX7 (every 2 weeks); mXELOX (oxaliplatin [day 1] + oral capecitabine [days 1–8] every 2 weeks); FOLFIRI (every 2 weeks); LV5-FU2 (400 mg/m^2 bolus and 2400 mg/m^2 46 hour infusion every 2 weeks); bevacizumab (5 mg/kg every 2 weeks); capecitabine (1250 mg/m^2 twice daily continuously); erlotinib (150 mg daily continuously)	The addition of erlotinib to bevacizumab maintenance therapy in patients with mCRC is not recommended; the combination demonstrated modest survival benefit and increased toxicity

(continued)

Table 8.5 (continued)

Maintenance trials	Agents used	Comments
MACRO-2 [77]	Cetuximab (250 mg/m^2 weekly); mFOLFOX6 (every 2 weeks)	Cetuximab maintenance therapy alone was non-inferior to cetuximab + FOLFOX maintenance therapy
NORDIC-7 [78]	Nordic FLOX (oxaliplatin 85 mg/m^2 on day 1, bolus 5-FU 500 mg/m^2, bolus FA 60 mg/m^2 on days 1 and 2, every 2 weeks); cetuximab (initial dose of 400 mg/m^2 and thereafter 250 mg/m^2, weekly)	Cetuximab maintenance therapy did not add significant benefit to the Nordic FLOX induction regimen
NORDIC-7.5 [79]	Nordic FLOX (oxaliplatin 85 mg/m^2 on day 1, bolus 5-FU 500 mg/m^2, followed by bolus FA 60 mg/m^2 on days 1 and 2, every 2 weeks); cetuximab (initial dose of 400 mg/m^2 and thereafter 250 mg/m^2, weekly)	In preselected *KRAS* WT patients, cetuximab could be safely integrated into an intermittent chemotherapy strategy: RR and PFS/OS rates were good
COIN-B [80]	FOLFOX (l-folinic acid 175 mg, oxaliplatin 85 mg/m^2, 400 mg/m^2 bolus and 2400 mg/m^2 46 hour infusion every 2 weeks); cetuximab (initial dose of 400 mg/m^2 and thereafter 250 mg/m^2, weekly)	In preselected *KRAS* WT patients, there was no difference in survival outcome between continuous (maintenance) cetuximab and intermittent cetuximab when administered with intermittent FOLFOX

FOLFOX Folinic acid, 5-fluorouracil, and oxaliplatin, *5-FU* 5-fluorouracil, *PFS* progression-free survival, *OS* overall survival, *RR* response rate, *FOLFIRI* folinic acid, 5-FU, and irinotecan, *XELOX* capecitabine and oxaliplatin

appropriate strategy for patients with advanced colon cancer because it not only improves patient quality of life but also improves sensitivity of the tumor(s) to oxaliplatin upon its reintroduction. A complete CFI is undesirable, but administration of maintenance leucovorin/5-FU during the oxaliplatin-free interval is effective. The authors concluded that initial sensitivity of the cancer to oxaliplatin is an important consideration when deciding upon this stop-and-go approach [81].

The idea of intermittent chemotherapy was also studied using irinotecan in a large-scale multicenter trial. In 2001 (published 2010), the GISCAD (Italian Group for the Study of Digestive Tract Cancers) trial was designed to determine the efficacy of intermittent irinotecan (Table 8.5) [71]. A total of 337 patients with advanced metastatic colon cancer were randomized into two groups. The "standard" arm (arm 1) received continuous 2-week cycles of FOLFIRI, whereas the "intermittent" arm (arm 2) received 2-week cycles of FOLFIRI for four cycles (2 months). Thereafter, in arm 2, treatment was discontinued for 2 months (a chemotherapy holiday). After the 2-month holiday, the initial regimen of 2-week cycles of FOLFIRI was administered for another four cycles (2 months). At the end of these 6 months, objective evaluation for disease progression was performed. If progression occurred during the chemotherapy break, a second-line treatment was given. Study results indicated that there was no difference in PFS (6 months for both arms; HR = 1.03, 95% CI = 0.81–1.29), objective response rate (42% for arm 1 vs. 34% for arm 2 [p = 0.192]), or tumor-growth control rate (76% for arm 1 vs. 67% for arm 2 [p = 0.104]). The 2-year OS rate was 30% for arm 1 and 34% for arm 2 (HR = 0.88, 95% CI = 0.69–1.14). Additionally, there was no difference in toxicity between arms. This study concluded that when using irinotecan and 5-FU, a chemotherapy-free interval is not inferior to continuous treatment. This study agreed with previous European study results: a chemotherapy holiday is very feasible for this regimen [71].

Bevacizumab and Combinations

As reported earlier, adding bevacizumab on the back of oxaliplatin regimens (FOLFOX or XELOX) or irinotecan regimens (FOLFIRI) has been shown to significantly increase the likelihood of a tumor response and increased patient survival.

Two phase III trials were carried out to test the use of bevacizumab alone as maintenance therapy:

- Investigators in the MACRO-TTD trial studied patients treated with frontline XELOX plus bevacizumab induction chemotherapy followed by maintenance therapy with continued XELOX plus bevacizumab or bevacizumab alone (Table 8.5). This study revealed no statistically significant differences in median PFS or OS between maintenance therapy with XELOX plus bevacizumab versus bevacizumab alone (PFS, 10.4 months vs. 9.7 months; OS, 23.2 months vs. 20 months). There were also no differences in RR. Initially set statistical limits did not allow for confirmation of non-inferiority between the two study arms [72].
- Investigators in the SAKK 41/06 trial, which was conducted at 26 sites in Switzerland, randomized patients who had just completed first-line chemotherapy to maintenance therapy with bevacizumab alone, versus no maintenance therapy (Table 8.5). Patients in the bevacizumab continuation arm received a median of six cycles of treatment. There was no statistically significant difference in median OS or time to progression (TTP) between the bevacizumab continuation arm and the no treatment arm (OS = 25.4 vs. 23.8 months and TTP = 4.1 vs. 2.9 months). Initially set limits did not allow for confirmation of non-inferiority between the two study arms [73].

Despite a lack of statistically significant results, many believe that maintenance therapy with single-agent bevacizumab could be an appropriate option following 4–6 months of standard first-line chemotherapy plus bevacizumab, although this cannot be confirmed at present.

There has generally been a lack of consensus regarding a role for maintenance therapy in the first-line setting. Thus the Dutch Colorectal Cancer Group (DCCG) set out to determine the efficacy of maintenance therapy versus just observation in their landmark prospective clinical trial known as CAIRO-3, results from which were published in April 2015 [74]. This was an open-label, randomized, phase III clinical trial involving collaboration of investigators across 64 hospitals within the Netherlands. After six cycles of CapeOx-Bev induction therapy, patients with stable disease or better were randomly assigned either to maintenance therapy with capecitabine plus bevacizumab or to observation (no treatment). The maintenance phase was initiated within 2 weeks of completion of the last induction cycle.

In the maintenance treatment group, a median of nine cycles of capecitabine and ten cycles of bevacizumab were administered. At 48 months of follow-up, median PFS (the primary endpoint) was 8.5 months in the observation group and 11.7 months in the maintenance treatment group, demonstrating a statistically significant superiority of maintenance treatment. Median OS was 18.1 months in the observation group and 21.6 months in the maintenance group. Overall, maintenance treatment was well tolerated, although the incidence of hand-foot syndrome was increased compared with the observation-only group. The global quality of life did not deteriorate during maintenance treatment and was not clinically different between treatment and observation groups. Hence this study revealed that maintenance treatment with capecitabine plus bevacizumab after six cycles of CapeOx-Bev in patients with mCRC was effective and did not compromise quality of life [74].

The 3-arm AIO-0207 trial, published in September 2015 [75], was another important study that was aimed at assessing the usefulness of maintenance therapy (Table 8.5). A fluoropyrimidine plus bevacizumab regimen was found to be a viable maintenance therapy option for patients with mCRC. Following 24 weeks of induction therapy with FOLFOX plus bevacizumab or CapeOx plus bevacizumab, the investigators assessed whether patients with no sign of disease progression further benefited from discontinuation of therapy, continuation with bevacizumab alone, or continuation with the chosen fluoropyrimidine plus bevacizumab regimen. The primary endpoint of the study was time to failure (TTF) of the maintenance strategy, defined as the time from randomization to second progression, death, or initiation of further treatment including a new drug. At the time of analysis, median follow-up from randomization was 17 months. Median TTF was 6.9 months for the fluoropyrimidine plus bevacizumab group, 6.1 months for the bevacizumab-alone group, and 6.4 months for the untreated group. Bevacizumab alone was non-inferior to standard fluoropyrimidine plus bevacizumab as maintenance therapy (HR = 1.08, $p = 0.53$), whereas therapy discontinuation was found to have a trend toward inferiority (HR = 1.26, $p = 0.056$). Both CAIRO-3 [74] and AIO-0207 [75] trials indicate that maintenance treatment with a fluoropyrimidine plus bevacizumab may be a reasonable option for patients with mCRC.

During the past decade, the management of patients with mCRC has improved due to the development of new therapies [82]. Inclusion of drugs targeting VEGF and EGFR in combination with chemotherapy has resulted in a mOS time of more than 30 months [8, 51]. Erlotinib, an EGFR tyrosine kinase inhibitor (TKI), has been less widely investigated in the treatment of mCRC [83]; however, evidence from preclinical models suggests that the combination of a TKI with bevacizumab might have synergistic activity [84]. The GERCOR DREAM (OPTIMOX3) trial assessed whether patients with unresectable mCRC benefited more from maintenance therapy with a combination of erlotinib and bevacizumab than they did from bevacizumab alone. This multicenter, 2-arm, open-label, randomized phase III trial was undertaken in 49 centers, and results were published in October 2015 [76]. Initially, patients were enrolled and randomized to 3 months of induction therapy with mFOLFOX7 plus bevacizumab or mXELOX plus bevacizumab, before being assigned to maintenance therapy (Table 8.5). The OPTIMOX1 and OPTIMOX2 trial data analyses were completed after initiation of the OPTIMOX3 trial on January 1, 2007, but once results came through indicating that 3 months of induction therapy were insufficient to justify complete chemotherapy cessation, the OPTIMOX3 protocol was amended (on Sept 19, 2008) to incorporate an extra 3 months of induction therapy, for a total of 6 months. Maintenance therapy with bevacizumab alone or bevacizumab plus erlotinib was assessed until patients experienced disease progression or unacceptable toxicity. In the final OPTIMOX3 analysis, median PFS was 5.4 months in the bevacizumab plus erlotinib arm compared with 4.9 months in the bevacizumab monotherapy arm (HR = 0.81, $p = 0.059$). The median OS of patients receiving maintenance therapy with bevacizumab plus erlotinib was 24.9 months, which was significantly greater than those receiving bevacizumab alone (22.1 months, $p = 0.036$). Despite the positive OS outcome, 47 of the 220 patients (21%) in the bevacizumab plus erlotinib arm vs. none of the 224 patients in the bevacizumab-alone arm experienced grade 3–4 skin rash, 21 (10%) vs. 2 (<1%) experienced diarrhea, and 12 (5%) vs. 2 (<1%) experienced asthenia. It was concluded that the addition of erlotinib to bevacizumab maintenance therapy in patients with mCRC was promising but at the expense of increased toxic-

ity [76]. This regimen is not currently recommended as standard maintenance treatment for patients with mCRC.

EGFR Inhibitors

There are data to support the incorporation of EGFR inhibitors into maintenance therapy. The multicenter MACRO-2, phase II, non-inferiority study enrolled previously untreated patients with *KRAS* WT exon 2 mCRC to receive eight cycles of mFOLFOX plus cetuximab before being randomized to continue on mFOLFOX/cetuximab therapy or switch to cetuximab maintenance therapy (Table 8.5). No statistically significant differences in PFS, objective response rate (ORR), or OS were seen between the two arms. A safety analysis revealed that both treatment regimens were reasonably tolerated. According to these findings, induction therapy with mFOLFOX plus cetuximab followed by maintenance therapy with cetuximab alone was not inferior to maintenance therapy with mFOLFOX plus cetuximab [77].

The landmark phase III multicenter NORDIC-7 trial investigated the efficacy of cetuximab in combination with bolus 5-FU/leucovorin plus oxaliplatin (Nordic FLOX) in the first-line treatment for patients with mCRC, followed by randomization of patients 1:1:1 to receive maintenance therapy with FLOX alone (arm A), cetuximab plus FLOX (arm B), or cetuximab plus intermittent FLOX (arm C) (Table 8.5). This trial also investigated the influence of patient tumor *KRAS* mutations (in codons 12 and 13, both in exon 2) and BRAF V600E mutations on treatment outcomes. In the intent-to-treat (ITT) population, mPFS was 7.9 (arm A), 8.3 (arm B), and 7.3 (arm C) months (no statistical differences), and OS was almost identical between the three groups (20.4, 19.7, 20.3 months, respectively). *KRAS* mutations were present in 39% of tumors, whereas *BRAF* mutations were present in 12% of tumors. The presence of *BRAF* mutations was found to be a strong negative prognostic factor. In patients with *KRAS* WT tumors, cetuximab did not provide any additional benefit compared with FLOX alone. In conclusion, according to this study, cetuximab did not add significant benefit to the Nordic FLOX regimen in first-line and maintenance treatment of mCRC [78].

Building upon arm C of the NORDIC-7 trial, the NORDIC-7.5 phase II trial aimed to further evaluate continuous cetuximab plus intermittent FLOX in the first-line treatment of 152 patients who were prospectively selected to have *KRAS* WT mCRC (Table 8.5). Patients received eight courses of Nordic FLOX, and the RR was 62%, the mPFS was 8 months, and the median OS was 23.2 months. Fourteen percent of patients underwent subsequent R0 resection of metastases. FLOX with cetuximab was reintroduced postsurgically in 55% of these patients. Grade 3/4 adverse event rates were low, including diarrhea (9%), skin rash (9%), infection without neutropenia (7%), and fatigue (7%). It was concluded that in preselected *KRAS* WT patients, biweekly cetuximab could be safely integrated into an intermittent chemotherapy strategy, thus lengthening the chemotherapy-free interval and improving OS [79].

COIN-B was another multicenter, randomized, phase II trial, which was carried out at 30 hospitals in the United Kingdom (Table 8.5) [80]. Patients with *KRAS* WT mCRC were randomized (1:1) to intermittent FOLFOX plus intermittent cetuximab or intermittent FOLFOX plus continuous cetuximab. Patients received their respective treatments for 12 weeks, after which they either underwent a planned treatment interruption (those taking intermittent cetuximab) or planned maintenance therapy involving continuing weekly cetuximab (those taking continuous cetuximab). Sixty-four patients in the intermittent cetuximab arm and 66 patients in the continuous cetuximab arm were included in the primary outcome analysis, which was failure-free survival at 10 months. Thirty-two patients (50%) in the intermittent cetuximab group and 34 patients (52%) in the continuous cetuximab group achieved this outcome. Median failure-free survival was 12.2 months and 14.3 months, respectively. The trial demonstrated that, in a molecularly selected (*KRAS* WT) population, maintenance of cetuximab monotherapy after treatment with cetuximab plus a less cytotoxic chemotherapy regimen within the first 6 months shows promise.

Summary

Many clinicians choose infusional 5-FU plus bevacizumab [75] or capecitabine plus bevacizumab [72, 74]. Specifically, the CAIRO-3 study approach is a favorite, which involves maintenance therapy with capecitabine plus bevacizumab following induction therapy with six cycles of CapeOx plus bevacizumab [74]. If everything is under control using this strategy, many physicians choose to give patients a complete break and just monitor them and restart the same regimen after a short period of time. We recommend an individual approach for patients in this setting to optimize control over the cancer while preserving their quality of life.

Second-Line Therapy

Patients are usually offered second-line therapy once their tumor starts progressing or they experience unacceptable toxicity on first-line therapy.

Chemotherapy

After a patient progresses on first-line therapy, the next treatment option is called second-line therapy (Table 8.6 [85–89]). FOLFOX6 and FOLFIRI have both been shown to improve

Table 8.6 Second-line trials in patients with mCRC

Second-line trials	Agents used	
ML18147 [85]	Bevacizumab (either 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks)	Continued bevacizumab therapy beyond disease progression, in combination with standard second-line chemotherapy, results in significantly better clinical response
VELOUR [86]	FOLFIRI; ziv-aflibercept (4 mg/kg)	In patients previously treated with oxaliplatin, a significantly better OS benefit was achieved using ziv-aflibercept in combination with FOLFIRI compared with placebo plus FOLFIRI
RAISE [87]	FOLFIRI; ramucirumab (8 mg/kg every 2 weeks)	Second-line mCRC treatment with ramucirumab plus FOLFIRI significantly improved patient OS compared with placebo plus FOLFIRI
BOND-1 [88]	Cetuximab 400 mg/mg^2 (loading dose) and then weekly 250 mg/m^2, with or without irinotecan	Cetuximab was effective when given alone or in combination with irinotecan
BOND-2 [89]	Cetuximab as in BOND-1, with bevacizumab 5 mg/kg every 2 weeks, with or without irinotecan	Adding bevacizumab to cetuximab or cetuximab + irinotecan yielded better OS than without bevacizumab In the absence of supporting studies, adding a VEGF plus EGFR inhibitor combination to chemotherapy should be practiced with caution

FOLFIRI Folinic acid, 5-fluorouracil, and irinotecan, *OS* overall survival, *VEGF* vascular endothelial growth factor, *EGFR* epidermal growth factor receptor

survival of patients with mCRC. In 2004, Tournigand et al. published a study to determine the first- and second-line sequencing of these treatment regimens (GERCOR [39]) in the management of mCRC. Two hundred twenty patients were randomized into two groups; they all had mCRC and were treatment naïve. In arm A, 109 patients were first treated with FOLFIRI until development of disease progression or toxicity, at which point they were switched to FOLFOX6. In arm B, 111 patients were first given FOLFOX6 until development of disease progression or toxicity when they were switched to FOLFIRI. Median OS for arm A was 21.5 months and for arm B was 20.6 months ($p = 0.99$, not significant). The primary objective of the study, "second PFS," was defined as the amount of time between randomization and progression of disease after initiating the second line of therapy. Second PFS was also not significantly different between the two different sequences: 14.2 months for arm A and 10.9 months for arm B ($p = 0.64$). Although there were no differences in OS, first PFS, second PFS, and response rates, there was a difference in toxicity profiles between the two arms. FOLFIRI administration led to more grade 3 and 4 mucositis, nausea, vomiting, and grade 2 alopecia, whereas FOLFOX6 was associated with more grade 3 and 4 neutropenia [39].

EGFR Inhibitors

Cetuximab

Numerous studies have been carried out to determine the most efficacious second-line therapy in the management of patients with mCRC. In 2004, the combination of cetuximab and irinotecan was studied in the BOND-1 trial [88]. Three hundred and twenty-nine patients (not enriched for RAS) who had disease progression on or within 3 months of an irinotecan regimen were randomized to cetuximab in combination with irinotecan or cetuximab alone. Response rates were significantly higher in the arm receiving cetuximab monotherapy (22.9% vs. 10.8%, $p = 0.007$). However, the median time to progression was greater in the cetuximab/irinotecan arm (4.1 months) than in the cetuximab monotherapy arm (1.5 months, $p < 0.001$). There was no significant difference in OS times: 8.6 months following combination therapy vs. 6.9 months with cetuximab alone, $p = 0.48$. As expected, patients in the combination arm experienced more adverse events than patients in the monotherapy arm. This study concluded that cetuximab had good clinical activity when given to patients with irinotecan-refractory cancer, either as a single agent or in combination with irinotecan. It should be kept in mind that this study was performed before the significance of *RAS* mutations came to light.

In another second-line treatment study by Jonker et al., published in 2007 [90], 572 patients who had mCRC that expressed EGFR were randomly divided into 2 groups. Every patient in the study had previously progressed on FOLFIRI or FOLFOX. One group was given weekly cetuximab with BSC, whereas the other group received BSC only (without any cancer-specific treatment). PFS, OS, and QOL were all improved in those patients receiving cetuximab. The OS following cetuximab treatment was 6.1 months vs. 4.6 months. Patient *KRAS* mutation status was unknown. Adverse events were greater in the cetuximab arm (78.5%) than in the BSC-alone arm (59.1%). However, the QOL measurements of physical function and global health status scores were better [90].

In May 2008, a phase III trial called the European Prospective Investigation into Cancer and Nutrition (EPIC) was published showing that, after progression on first-line fluoropyrimidine and oxaliplatin treatment, the addition of

cetuximab to irinotecan in the second line is superior to irinotecan alone. Patients who had tumor progression on a fluoropyrimidine plus oxaliplatin regimen were recruited into this study if they also had evidence of EGFR expression. Patients may have previously been treated with bevacizumab but not irinotecan or any anti-EGFR therapy. In the second-line setting, 1298 patients were randomized 1:1 to receive irinotecan plus cetuximab (arm 1) or irinotecan alone (arm 2). In both arms, irinotecan was given at a dose of 350 mg/m^2 every 3 weeks. In arm 1, cetuximab was administered as a 400 mg/m^2 loading dose on day 1, followed by 250 mg/m^2 weekly. PFS was significantly better in the cetuximab/irinotecan arm (4.0 months) than in the irinotecan-only arm (2.6 months, $p < 0.0001$). There was no significant difference in mOS between the two groups (10.7 months vs. 10.0 months [p = 0.71]). The overall RR was significantly higher in the combination arm (16.4%) than in the cetuximab-only arm (4.2%, $p < 0.0001$). The most common toxicities following cetuximab/irinotecan treatment were diarrhea, nausea, fatigue, and acneiform rash. Single-agent irinotecan treatment yielded the same toxicity pattern with the exception of acneiform rash [91].

Panitumumab

A phase III trial carried out by Peeters et al. addressed whether the addition of panitumumab to second-line FOLFIRI improved PFS and OS in patients with mCRC [7]. The study enrolled 1186 patients who had experienced disease progression on previous fluoropyrimidine-based chemotherapy regimens. These patients were randomized 1:1 to receive FOLFIRI plus panitumumab (6 mg/kg) vs. FOLFIRI alone; treatment was administered on a 2-week cycle [7]. The investigators also stratified the patient groups according to their KRAS tumor status: either mutant or WT. They found that in KRAS WT patients, there was a significant improvement in PFS for those who received panitumumab: 5.9 months vs. 3.9 months (p = 0.004). The OS was also increased, but not significantly (14.5 months vs. 12.5 months). However, patients with KRAS-mutated tumors did not show any change in PFS, OS, or RR with the addition of panitumumab.

Thus, the study by Peeters et al. supports the use of panitumumab plus FOLFIRI in the second-line treatment of patients with *KRAS* WT mCRC [7, 47].

Another trial evaluated panitumumab in the second-line setting in combination with irinotecan. Thus, the phase III PICCOLO trial randomized patients to three treatment arms: irinotecan, irinotecan plus panitumumab, and irinotecan plus ciclosporin [92]. A year and a half into the study, the trial was amended to allow randomization of only patients with *KRAS* WT tumors to the panitumumab arm; thus patients with *KRAS* WT mCRC who had not received any anti-EGFR therapy and had progressed on fluoropyrimidine-based chemotherapy were enrolled. Here, we discuss results from the irinotecan and irinotecan plus panitumumab arms of the trial in *KRAS* WT patients only. Thus, 460 patients with *KRAS* WT tumors were randomized 1:1 to receive irinotecan (350 mg/m^2) alone or in combination with panitumumab (9 mg/kg) every 3 weeks [93]. Regarding safety, the addition of panitumumab to irinotecan increased the following grade 3 and higher adverse events: diarrhea (29% vs. 18%), skin toxicity (19% vs. 0%), lethargy (21% vs. 11%), infection (19% vs. 10%), and hematologic toxicity (22% vs. 12%).

Regarding efficacy, significant improvements in median PFS (HR = 0.78, p = 0.015) and ORR (odds ratio [OR], 4.12, $p < 0.0001$) were observed with the addition of panitumumab to irinotecan. Again, OS was not significantly different between the two arms. However, a partial response (PR) was observed in 33% of patients 12 weeks after initiation of treatment with panitumumab plus irinotecan, and 1% had a complete response (CR). These RRs are much higher than those seen in the irinotecan-only-treated patients: 12% had a PR at 12 weeks and none had a CR.

In conclusion, both second-line panitumumab treatment studies of *KRAS* WT patients [7, 47, 92, 93] show no OS benefit to adding panitumumab to irinotecan or FOLFIRI, despite an initial improvement in disease response and PFS.

VEGF Inhibitors

Bevacizumab

Bevacizumab plus fluoropyrimidine-based chemotherapy is the standard treatment for first-line and bevacizumab-naïve second-line mCRC. The ML18147 trial assessed continued use of bevacizumab with standard second-line chemotherapy in patients who had progressed during or within 3 months of the last dose of standard first-line bevacizumab-based treatment. Patients were randomly assigned to receive second-line chemotherapy with or without bevacizumab. The choice between oxaliplatin-based or irinotecan-based second-line chemotherapy depended on the first-line regimen (switch of chemotherapy). Median OS in this trial was 11.2 months for patients treated with bevacizumab plus chemotherapy and 9.8 months for patients treated with chemotherapy alone (HR = 0.81, p = 0.0062). Grade 3/4 toxicities were similar in both groups, except that venous thromboembolisms were more common in the bevacizumab arm (5% vs. 3%). From this study we can deduce that continued VEGF inhibition with bevacizumab in combination with standard second-line chemotherapy beyond disease progression has clinical benefits in patients with mCRC [85].

Aflibercept

Investigators conducting the VELOUR trial studied the effect of adding the more novel antiangiogenic agent ziv-aflibercept

to FOLFIRI in patients with mCRC previously treated with oxaliplatin, including patients who had received prior bevacizumab. Patients were randomly assigned to receive ziv-aflibercept or placebo every 2 weeks in combination with FOLFIRI. It was shown that adding ziv-aflibercept to FOLFIRI significantly improved mOS compared with placebo plus FOLFIRI (13.5 months vs. 12 months; HR = 0.817, $p = 0.0032$). Ziv-aflibercept also significantly improved PFS (6.9 months vs. 4.6 months; HR = 0.758, $p = 0.0001$). There was a consistent trend in OS and PFS across pre-specified subgroup analyses, including bevacizumab-pretreated patients. In this case, response rates were 19.8% for ziv-aflibercept plus FOLFIRI, compared with 11.1% for placebo plus FOLFIRI ($p = 0.0001$). Adverse events reported following ziv-aflibercept plus FOLFIRI treatment included the characteristic anti-vascular endothelial growth factor effects (arterial and venous thromboembolic events, hypertension, and proteinuria), as well as an increased incidence of some chemotherapy-related toxicities. It was concluded from this study that ziv-aflibercept in combination with FOLFIRI conferred a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin [86].

EGFR and VEGF Inhibitor Combinations

In 2007, investigators conducting the BOND-2 study divided 83 patients already treated with an irinotecan-containing regimen into 2 arms: arm A received cetuximab (400 mg/m^2 [loading dose] followed by 250 mg/m^2 cetuximab weekly) plus bevacizumab (5 mg/kg every other week) plus irinotecan (at pre-study doses); arm B received identical cetuximab and bevacizumab treatment to arm A, but without irinotecan. Arm A had a median OS of 14.5 months versus 11.4 months for arm B. The time to progression was 7.3 months and 4.9 months in arms A and B, respectively. The toxicities were as expected in that they were similar to toxicities from each agent alone. This trial showed that adding bevacizumab to either cetuximab or cetuximab plus irinotecan yielded better OS than cetuximab or cetuximab plus irinotecan without bevacizumab [89].

Although other studies of EGFR and VEGF inhibitor combinations took place in the first-line and not the second-line setting, those other studies do seem to suggest that combining anti-VEGF and anti-EGFR antibodies is detrimental to patients undergoing cancer therapy, or at least not helpful. The PACCE study [18] and the CAIRO2 trial [19] are thus discussed in the "First-Line Therapy" section of this chapter.

Ramucirumab

Ramucirumab, a human immunoglobulin G1 (IgG1) monoclonal antibody that targets the extracellular domain of VEGF receptor 2, was assessed in the phase III RAISE trial, which evaluated the efficacy and safety of ramucirumab versus placebo in combination with second-line FOLFIRI for mCRC in patients with disease progression during or within 6 months of the last dose of first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Median OS, the primary study endpoint, was 13.3 months in ramucirumab-treated patients versus 11.7 months in the placebo group (HR = 0.844, $p = 0.0219$). Survival benefit was consistent across subgroups of patients who received ramucirumab plus FOLFIRI. A significant ramucirumab-induced elevation of grade 3/4 toxicities was seen for neutropenia (38% in the ramucirumab group vs. 23% in the placebo group) and hypertension (11% vs. 3%). The study investigators concluded that second-line mCRC treatment with ramucirumab plus FOLFIRI significantly improved patient OS compared with placebo plus FOLFIRI. Observed adverse events were as expected and manageable [87].

Third-Line Therapy

Third-line treatment choices are available and include chemotherapy, targeted agents, and clinical trial options, as well as palliative care. Palliative care will be discussed first because patient outcomes following novel treatment modalities are often compared with this approach.

Palliative Care

The aim of palliative care, also known as the best supportive care [94], is not to cure but to relieve cancer-related symptoms and/or treatment-related side effects. A patient or care team can choose palliative care at any point during a patient's disease course, and most believe it should begin at diagnosis and continue throughout the treatment period; however, this type of care is most known for its use at the end of a patient's life when all possible curative treatments have failed.

EGFR Inhibitors and Chemotherapy

Relatively non-aggressive systemic therapy options beyond the best supportive care have been attempted to see if there is an improvement in longevity or quality of life at the end of life. In a phase III CA225025 trial by Jonker et al., 572 patients with previously treated EGFR-expressing advanced CRC were randomized 1:1 to receive BSC or BSC plus cetuximab (400 mg/m^2 IV loading dose administered over 120 minutes followed by 250 mg/m^2 over 60 minutes weekly) [90]. The ability of cetuximab to improve OS of patients with advanced CRC who had failed all other treatments (fluoropy-

rimidine, irinotecan, and oxaliplatin) or had contraindications to treatment with these drugs was assessed. In fact, cetuximab was seen to improve OS in comparison with BSC alone (HR for death = 0.77, 95% CI = 0.64–0.92, $p = 0.005$). The median survival of patients treated with cetuximab was 6.1 months versus 4.6 months in patients receiving BSC only. Although patients completed a QOL questionnaire, the interpretation of these questionnaires is historically difficult [95]. In this particular study, more rapid disease progression, which was observed in the BSC group, resulted in a lower QOL questionnaire-compliance rate [90]. As may be expected, disease response to treatment contributed to a relatively improved QOL in the cetuximab arm compared with the BSC-alone arm, even though patients in the cetuximab arm had a higher rate of rash (88.6% vs. 16.1%, $p < 0.001$), hypomagnesemia (53.3% vs. 15.1%, $p < 0.001$), and infusion reactions (20.5% vs. 0%, $p < 0.001$) [90]. Thus, it is unreasonable to use tumor response alone as a surrogate for QOL.

In a phase III trial by Van Cutsem et al., 463 patients with EGFR-expressing mCRC, who had failed 2 or more prior lines of chemotherapy, were randomized 1:1 to receive BSC or BSC plus panitumumab (6 mg/kg IV over 60 minutes every 2 weeks) until disease progression or treatment intolerance [96]. Although there was no statistically significant difference in mOS (HR = 1.00, 95% CI = 0.82–1.22, $p = 0.81$), mPFS following panitumumab was greater than that following BSC alone (8.0 vs. 7.3 months; HR = 0.54, 95% CI = 0.44–0.66, $p < 0.0001$), and 175 patients in the BSC arm crossed over to the panitumumab arm. Regarding adverse events, 90% of patients in the panitumumab arm had skin toxicity compared with 9% in the BSC group.

Of course, since these EGFR inhibitor studies were carried out, it has been emphasized that only patients with *RAS* and *BRAF* WT tumors can be expected to respond to this type of therapy.

The ASPECCT trial set out to compare cetuximab with panitumumab in the treatment of patients ($n = 1010$) with chemotherapy-refractory *KRAS* WT mCRC. Patients were randomized 1:1 to receive panitumumab or cetuximab monotherapy, and at the end of the study, panitumumab was found to be non-inferior to cetuximab: thus, the median OS was 10.4 months with panitumumab and 10.0 months with cetuximab (no significant difference). Although panitumumab led to higher rates of hypomagnesia, both antibodies led to grade 3 and 4 skin toxicities and infusion reactions. The conclusion was that both agents are effective in the second-line treatment of mCRC, and the choice between the two should be made on the basis of toxicity profiling and dose scheduling [97].

Generally, third-line treatment of patients with *RAS* (and *BRAF*) WT tumors with anti-EGFR therapies should always be considered. Chemotherapy options that can be considered regardless of tumor mutation status include irinotecan or 5-FU-based regimens (infusional 5-FU plus leucovorin or capecitabine) with or without bevacizumab. Individual treatment decisions depend on prior therapy received. If a patient has not already received or responded well to any particular standard chemotherapy agent, its use should be considered in the third line [98, 99]. More novel therapies, such as regorafenib and TAS-102, should also be considered, and these are discussed later. Due to the adverse event potential of chemotherapy, physicians must comprehensively discuss with their patients the risks and benefits of chemotherapy compared with BSC. Ultimately, the treatment decision should be made collaboratively between patient and physician. If chemotherapy is chosen, patient health should be monitored carefully.

Regorafenib

Several promising new therapies have emerged for patients with refractory mCRC. Refractory patients include those who have previously been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, as well as anti-VEGF and anti-EGFR (*RAS* WT only) biological therapies.

In 2012, the FDA approved regorafenib, an oral multikinase inhibitor, for the treatment of patients with mCRC who have failed multiple lines of therapy, including fluoropyrimidine, oxaliplatin, irinotecan, and anti-VEGF and/or anti-EGFR therapy (in patients who were *KRAS* WT). Regorafenib blocks the activity of receptor tyrosine kinases involved in tumor angiogenesis, oncogenesis, and tumor microenvironmental signaling pathways. This includes VEGFR1/2/3, the platelet-derived growth factor receptor-b (PGFR), the fibroblast growth factor receptor (FGFR), TIE2, c-KIT, RET, BRAF, and RAF1 [100].

The phase III double-blinded CORRECT trial was carried out at 114 centers in 16 countries in North America, Europe, Asia, and Australia. Patients with mCRC were randomized in a 2:1 ratio to 160 mg oral regorafenib or placebo, daily [101]. Patients were eligible for the study if they had received all locally available standard therapies and had either failed their most recent line of treatment due to disease progression or severe side effects (or both) or had progressive disease within 3 months of discontinuing their last line of treatment. Standard therapy classification varied by country, but previous standard treatments had to include the following as long as they were licensed for the treatment of CRC: fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab (in patients with *KRAS* WT tumors). In total, 760 patients were enrolled into the study, the primary and secondary endpoints of which were, respectively, survival and disease response to therapy (assessed by radiological surveillance every 8 weeks).

The mOS was 6.4 months in the 505 patients treated with regorafenib and 5 months in the 255 patients assigned to placebo (HR = 0.77, 95% CI = 0.64–0.94, $p = 0.0052$). Subset analysis indicated that regorafenib treatment is more effective in patients with colon cancer (mOS, regorafenib vs. placebo; HR = 0.70, 95% CI = 0.56–0.89) than in those with rectal cancer (HR = 0.95, CI = 0.63–1.43).

A complete response was not elicited in any of the patients; however, five patients in the regorafenib group and one patient in the placebo group had a partial response ($p = 0.19$). Disease control (partial response plus stable disease assessed at least 6 weeks after randomization) was observed in 41% of patients assigned to regorafenib and 15% of patients assigned to placebo ($p < 0.0001$).

Grade 3 or 4 adverse events occurred in 54% of the patients in the regorafenib group compared with 14% in the placebo group. The most common regorafenib-associated side effects were fatigue and hand-foot syndrome. Elevated transaminases and bilirubin were also more commonly seen with regorafenib, and one case of fatal hepatic failure was reported.

The CONCUR trial was another phase III trial, which was conducted in 25 centers in Asia [102]. In this double-blinded study, 204 patients with mCRC were randomly assigned in a 2:1 ratio to regorafenib or placebo. Patients were required to have received at least two lines of prior standard treatment, although individuals were less likely to have been treated with a VEGF-targeted or EGFR-targeted biological agent than patients in the CORRECT trial (60% [CONCUR] vs. 100% [CORRECT]). Median OS was 8.8 months in the regorafenib group compared with 6.3 months in the placebo group (one-sided $p = 0.0002$). Disease control was achieved in 51% of patients in the regorafenib arm, compared with 7% in the placebo arm (one-sided $p < 0.0001$). Subgroup analysis for colon cancer vs. rectal cancer patients was not carried out. Drug-related toxicity was similar to that seen in the CORRECT trial. Of the patients in the regorafenib arm, 54% had at least one grade 3 or higher drug-related adverse event, most commonly hand-foot skin reaction (16%) and hypertension (11%). Elevated transaminases and bilirubin were also recorded.

Approval of regorafenib has not been without controversy. In an editorial accompanying the CONCUR trial publication, the approval of this drug was questioned, given its high cost, heavy side effect profile, and relatively scant benefit. A 2015 cost-benefit analysis of the drug strengthened this argument, showing that regorafenib provided only 0.04 quality-adjusted life years at a cost of $40,000 [103].

TAS-102

Trifluridine/tipiracil (TAS-102; trade name Lonsurf) is the second drug to recently receive FDA approval for use in refractory CRC. It is an oral combination of trifluridine—a thymidine-based nucleic acid analogue—and tipiracil hydrochloride, a thymidine phosphorylase inhibitor (TPI). Trifluridine was first synthesized by Heidelberger et al. in 1962 [104]. Initial studies carried out in the 1960s were halted due to trifluridine's side effect profile and poor pharmacokinetics [105]. Trifluridine is phosphorylated by thymidine kinase-1 to its active monophosphate derivative, which reversibly inhibits thymidine synthetase (TS) [106]. TS plays an integral role in DNA synthesis by converting deoxyuridine 5-monophosphate (dUMP) to deoxythymidine-5′-monophosphate (dTMP) [107]. Unlike 5-FU, which forms a stable tertiary complex with TS and 5,10-methylenetetrahydrofolate, trifluridine has reversible, short-lived effects on TS, allowing the enzyme to rapidly recover upon clearance of the drug [105]. However, trifluridine's monophosphate form is further phosphorylated to its triphosphate form, and this triphosphate form has a second mechanism of action via its incorporation into DNA during DNA synthesis, leading to DNA strand breaks and tumor cell demise [108]. This is likely the main mechanism of action of the drug [108], which is probably responsible for trifluridine's activity in 5-FU-resistant disease [105]. Trifluridine has an extremely short half-life (18 minutes) when given intravenously, and it is rapidly degraded in its oral form due to first-pass metabolism by thymidine phosphorylase in the intestine and liver [106]. This is where tipiracil comes in; this second major component of TAS-102 prevents the rapid degradation of trifluridine by potently inhibiting thymidine phosphorylase [109]. Tipiracil may also have antineoplastic effects [106]. Thus TAS-102 is a viable cancer treatment.

Several phase I trials established the optimal dose and dosing schedule of TAS-102, which is 35 mg/m^2 twice daily for 5 days with a 2-day rest weekly for 2 consecutive weeks, followed by 2 drug-free weeks (28-day cycle) [110]. Between August 25, 2009, and April 12, 2010, a multicenter, double-blind, randomized, phase II trial was conducted in Japan, during which 169 patients were randomly assigned in a 2:1 ratio to TAS-102 versus placebo [111]. All patients had pathologically proven unresectable metastatic colorectal adenocarcinoma; had failed two or more regimens of standard chemotherapy; and were refractory to or intolerant of fluoropyrimidine, irinotecan, and oxaliplatin. The mOS in the TAS-102 group was 9.0 months (95% CI = 7.3–11.3) vs. 6.6 months (95% CI = 4.9–8.0) in the placebo group (HR = 0.56, 95% CI = 0.39–0.81, $p = 0.0011$).

These phase II results led to the RECOURSE trial, which was a double-blinded phase III study in which patients in the United States, Europe, Japan, and Australia were randomized in a 2:1 ratio to TAS-102 versus placebo [112]. Patients were eligible for the study if they had biopsy-proven metastatic adenocarcinoma of the colon or rectum and had received at least two prior lines of standard therapy, which

could include adjuvant therapy if disease progression had occurred within 6 months of its administration. Standard therapy included a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab (for patients with *KRAS* WT tumors). Radiological assessment was conducted every 8 weeks. The primary endpoint was OS.

Of the 800 patients recruited into this trial, 534 were randomized to receive TAS-102, and 266 were assigned to placebo. Median OS in the TAS-102 group was 7.1 months (95% CI = 6.5–7.8) vs. 5.3 months (95% CI = 4.6–6.0) in the placebo group. The hazard ratio for death (TAS-102 vs. placebo) was 0.68 (95% CI = 0.58–0.81, $p < 0.001$). Eight patients in the TAS-102 group had a partial response, but no complete response was recorded. In the TAS-102 group, 44% of patients achieved disease control compared with only 16% in the placebo group ($p < 0.001$). A grade 3 or higher adverse event was documented in 69% of patients in the TAS-102 group compared with 52% in the placebo group. The major adverse events (grade 3 or higher) in the TAS-102-treated patients were neutropenia (38%), anemia (18%), thrombocytopenia (5%), and alopecia (7%). Grade 3 or 4 stomatitis, hand-foot syndrome, and coronary artery spasm, all of which are a risk in patients treated with fluoropyrimidines, were encountered in less than 1% of patients treated with TAS-102 [112].

On the basis of these results, in September 2015, the FDA approved TAS-102 specifically for the treatment of patients with mCRC refractory to fluoropyrimidines, oxaliplatin, irinotecan, anti-VEGF therapy, and anti-EGFR therapy (in *RAS* WT patients).

Novel Therapies

Immunotherapy

In recent years, exciting advances have been made regarding immunotherapy as an oncologic treatment for solid tumors. Immune checkpoint inhibitors are revolutionizing the treatment of many metastatic tumors, including melanoma, lung, and kidney cancers.

It has been hypothesized that immunotherapy might be effective in the 3–6% of mCRC patients with mismatch repair-deficient (dMMR) disease [113]. dMMR tumors have 10–100 more somatic mutations than mismatch repair-proficient tumors and frequently have lymphocyte infiltration, suggesting immune system recognition. Some studies have suggested higher PD-L1 (programmed death ligand one) expression in dMMR tumors, which may mean increased sensitivity to checkpoint inhibitors [113].

In order to test the mismatch repair hypothesis, a phase II trial was conducted to examine the effect of pembrolizumab (a programmed death receptor [PD-1] antagonist) on patients with either sporadic or hereditary dMMR mCRC ($n = 11$), mismatch repair-proficient mCRC ($n = 21$), or other dMMR metastatic cancers ($n = 9$) [114]. Pembrolizumab was administered at a dose of 10 mg/kg IV every 14 days. Radiographic surveillance was performed after the first 12 weeks and then every 8 weeks thereafter. The primary endpoints of the study were immune-related ORR and immune-related PFS at 20 weeks.

In the dMMR colorectal group, the immune-related ORR (using Response Evaluation Criteria in Solid Tumors [RECIST] criteria) at 20 weeks was 40% (four of ten patients; 95% CI = 12–74), and the immune-related PFS rate at 20 weeks was 78% (seven of nine patients; 95% CI = 40–97%). In the cohort of patients with non-colorectal dMMR tumors, immune-related ORR and immune-related PFS at 20 weeks were 71% (five of seven patients; 95% CI = 29–96%) and 67% (four of six patients; 95% CI = 22–96%), respectively. Among patients with mismatch repair-proficient tumors, the ORR was 0% (95% CI = 0–20%), and the immune-related PFS rate at 20 weeks was 11% (2 of 18 patients; 95% CI = 1–35) [114].

In this study, response to treatment was also followed using tumor markers. Twenty-nine out of 32 patients had elevated CEA levels on trial initiation. Patients with disease progression showed further biomarker elevation within 30 days of starting therapy. On the other hand, decreased CEA levels appeared to predict response to treatment, often preceding the radiologic response by several months. CEA levels showed a downward trend in 70% (seven out of ten) of the patients with dMMR CRC, whereas none of the evaluable patients with mismatch repair-proficient CRC showed a decrease in CEA.

Median PFS and OS of patients in the dMMR groups had not been reached at the time of publication. Post hoc comparison of the dMMR and mismatch repair-proficient CRCs showed a hazard ratio for disease progression (HR = 0.10 [95% CI = 0.03–0.37]; $p < 0.001$) and death (HR = 0.22 [95% CI = 0.05–1.00]; $p = 0.05$) that favored patients with dMMR CRC.

Nivolumab has also shown immunotherapeutic benefit in mCRC patients with dMMR disease. The CheckMate-142 trial was an open-label, phase II study of patients with dMMR/MSI-H colon cancer, carried out across 31 sites in 8 different countries [28]. Eligible patients had progressed on or after or been intolerant of at least one previous line of treatment, including a fluoropyrimidine plus oxaliplatin or irinotecan. Nivolumab, at a dose of 3 mg/kg, was administered every 2 weeks until disease progression, death, unacceptable toxicity, or withdrawal from study. The median follow-up time was 12 months at the time of publication, and 23 of 74 patients (31.1%, 95% CI = 20.8–42.9) had achieved an investigator-assessed objective response, whereas 51 (69%, 57–79) patients had experienced disease control for 12 weeks or longer. Eight patients had responses lasting 12 months or longer, and median duration of response had

not yet been reached. Responses were seen regardless of PD-L1 expression level or *BRAF* and *KRAS* mutation status.

Anti-PD-1 therapy appears to be a very promising treatment for patients with dMMR tumors, and nivolumab and pembrolizumab are now FDA approved based mainly on the above data. Combined immunotherapy trials and trials examining earlier course treatment are currently underway.

BRAF Inhibition

Another exciting area of research involves targeted therapy against BRAF-mutated CRC. BRAF is a serine/threonine-protein kinase that is a key component in the MAPK/ERK signaling pathway, playing an important role in cellular growth, proliferation, and survival [115]. The most common BRAF mutation is the substitution of glutamic acid for valine at codon 600 (V600E). The second most common mutation is the BRAF V600K mutation, in which valine is replaced by lysine. BRAF mutations are present in 5–15% of colon cancers [116]. These tumors arise from the alternative sessile serrated adenoma pathway of colon cancer [117]. This differs from the classic pathway in which carcinomas arise from adenomas secondary to adenomatous polyposis coli (APC) mutations. BRAF-mutated tumors are generally poorly differentiated and have a high frequency of node-positive disease and peritoneal metastases [118]. These tumors also have characteristic molecular patterns, including microsatellite instability, hypermethylation, and minimal chromosomal instability [116]. Patients with mutated tumors have a poor prognosis and a median survival of 12 months in the metastatic setting [118]. Furthermore, a recent meta-analysis examining the effects of the EGFR inhibitors cetuximab and panitumumab in patients with BRAF-mutated tumors showed no PFS or OS benefits [119].

BRAF inhibitors (dabrafenib and vemurafenib) have been FDA approved in the treatment of metastatic melanoma after showing significant benefit compared with chemotherapy (dacarbazine) in phase III trials [115]. Two recent phase II trials have looked at BRAF inhibitor treatment in metastatic colon cancer patients with V600 mutated disease.

Thus, Kopetz et al. examined 21 patients who had received at least one standard of care treatment for metastatic disease and had confirmed V600E BRAF mCRC [116]. Vemurafenib was given at the previously determined maximum-tolerated dose of 960 mg twice a day, continuously in 28-day cycles. Response was assessed radiographically every two cycles or more frequently at the treating physician's discretion. There were no complete responses. One patient had a partial response for 21 weeks and seven others had stable disease (range 8–50 weeks). The mPFS was 2.1 months (range, 0.4 to 11.6 months) and the mOS was 7.7 months (range, 1.4 to 13.1 months). This compares favorably with cetuximab as monotherapy, which yielded a mOS in the second-line setting of 6.1 months (compared with 4.6 months following BSC).

In a second study, by Corcoran et al., 43 patients with V600E or V600K mCRC were treated with dabrafenib plus the MEK inhibitor, trametinib [120]. Previous systemic therapies received by trial participants ranged from none to greater than three treatments. This combination had shown promising results in melanoma compared with dabrafenib alone, with a significant improvement in PFS (11.0 vs. 8.8 months, $p = 0.0004$) and OS (25.1 vs. 18.7 months $p = 0.012$). Of the 43 CRC patients in this study, one patient who had not received prior therapy achieved a complete response for at least 36 months. An additional 4 patients (9%) achieved a partial response, and 24 patients (56%) had stable disease. Median PFS was 3.5 months.

Neither of the studies carried out in CRC patients by Corcoran et al. or Kopetz et al. achieved the results seen in melanoma. Corcoran et al. suggested that this discrepancy was due to decreased MAPK/ERK inhibition compared with melanoma. Paired pretreatment and day 15 treatment biopsies were available for 9 of the 43 CRC patients in Corcoran's study, and all 9 tumors showed a mean P-ERK decrease from baseline of 47%, which was significantly smaller than the 75% decrease seen in melanomas from patients treated with dabrafenib alone ($p < 0.001$).

Trials examining BRAF inhibitors combined with known efficacious therapies for metastatic colon cancer are also being examined. In the SWOG 1406 trial led by Kopetz et al. [121], the BRAF inhibitor vemurafenib (Zelboraf) was combined with cetuximab and irinotecan in patients with *BRAF* V600 mutated and extended *RAS* WT mCRC. Patients who had failed at least one line of therapy were randomized to irinotecan (180 mg/m^2 IV every 14 days) and cetuximab (500 mg/m^2 IV every 14 days) with or without vemurafenib (960 mg PO twice daily). Patients who had previously been on an anti-EGFR inhibitor were excluded from the trial. There were 106 patients enrolled including 54 in the experimental arm. The primary endpoint of PFS improved with the addition of vemurafenib (HR = 0.42, 95% CI = 0.26–0.66, $p < 0.001$): the mPFS was 4.4 months (95% CI = 3.6–5.7) vs. 2.0 months (95% CI = 1.8–2.1). Response rate was 16% vs. 4% ($p = 0.09$), with a disease control rate of 67% vs. 22% ($p < 0.001$).

Human Epidermal Growth Factor Receptor 2 Antagonists

A significant proportion of patients do not respond to the EGFR inhibitors cetuximab and panitumumab, and most patients who initially respond generally relapse after less than a year [6, 9]. About 70% of EGFR inhibitor-resistant patients carry a mutation in one of four kinase genes (*KRAS*, *NRAS*, *BRAF*, and *PI3K*) [122]. Efforts are underway to

identify mechanisms of resistance in the 30% of non-responders who carry the wild-type kinase genes.

Recent evidence suggests that overexpression of human epidermal growth factor receptor 2 (HER-2) may be involved in resistance to EGFR inhibitors [122]. HER-2 is overexpressed in approximately 15–30% of breast and 10–30% of gastric cancers [123], and administration of trastuzumab, a monoclonal antibody against the extracellular domain of HER-2, produced a significant survival benefit in patients with these HER-2-overexpressing breast and gastric cancers [124, 125]. As HER-2 is overexpressed in approximately 6% of CRC patients [126], there is some interest in combining anti-HER-2 and anti-EGFR therapies in this patient group.

Bertotti et al. recently conducted a trial of xenograft cohorts from patients with mCRC [29]. From these cohorts the investigators selected HER-2-overexpressed grafts to see whether HER-2 blockade would improve sensitivity to EGFR antagonists. The most promising treatment arms were cetuximab plus lapatinib (an antagonist against HER-2 and EGFR) and lapatinib plus pertuzumab (an antibody that disrupts HER-2 heterodimerization).

Based on these results, the investigators carried out an open-label, phase II trial (HERACLES) at four academic cancer centers in Italy [127]. Eligible patients were required to have mCRC with *KRAS* exon 2 (codons 12 and 13) WT and HER-2-positive disease that had progressed while on or within 6 months of standard therapy. All patients were required to have previously received fluoropyrimidines, oxaliplatin, irinotecan, and cetuximab or panitumumab. Patients had received a median of five treatments prior to study enrollment. Between August 2012 and May 2015, 27 patients were enrolled to receive a combination of lapatinib plus trastuzumab. With a median follow-up of 96 weeks, eight patients achieved an overall objective response. Median PFS was 21 weeks (95% CI = 16–32), and mOS calculated post hoc was 46 weeks (95% CI = 33–68), with 45% of patients alive at 1 year. One patient experienced a complete response, 7 achieved a partial response, and an additional 12 patients had stable disease. Common side effects included diarrhea (78%), rash (48%), fatigue (48%), paronychia (33%), and conjunctivitis (19%). A follow-up trial by the HERACLES group (HERACLES B) is examining pertuzumab in combination with trastuzumab emtansine in HER-2-positive colorectal cancer as a way to further improve efficacy in this group of patients [128].

Conclusion

In the last 20 years, we have transformed mCRC from an essentially hopeless disease to a disease that presents multi-agent, multimodality treatment pathways, the exploitation of which has almost tripled patient OS. Each physician team must know the pathologic, histologic, and molecular details of mCRC, as well as the treatment options available for the different disease stages and types, which include surgery, radiation therapy, systemic drug and biological agent therapy, and palliative care. Physicians should know how to optimize treatment using aggressive therapies when responses are needed and when to use less toxic maintenance therapies when preservation of stable disease is acceptable. The treatment of mCRC, like running a marathon, requires patience, endurance, intelligence, and the ability to read the ever-changing conditions. We hope this review of specific research studies and progress that the research community has made serves as a useful guide in the management of your next marathon race.

References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, et al. The global burden of cancer 2013. JAMA Oncol. 2015;1(4):505–27.
2. 2018. ACSCFFAACS. Available from: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018.html. 2018.
3. Cancer of the colon and rectum – seer stat fact sheets [database on the Internet] 2015. Available from: http://seer.cancer.gov/statfacts/html/colorect.html.
4. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/archive/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.
5. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. Folfoxiri plus bevacizumab versus folfiri plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 tribe study. Lancet Oncol. 2015;16(13):1306–15.
6. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408–17.
7. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase iii study of panitumumab with fluorouracil, leucovorin, and irinotecan (folfiri) compared with folfiri alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28(31):4706–13.
8. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. Folfiri plus cetuximab versus folfiri plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (fire-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(10):1065–75.
9. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase iii trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (folfox4) versus folfox4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the prime study. J Clin Oncol. 2010;28(31):4697–705.

10. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. Peak: a randomized, multicenter phase ii study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mfolfox6) or bevacizumab plus mfolfox6 in patients with previously untreated, unresectable, wild-type kras exon 2 metastatic colorectal cancer. J Clin Oncol. 2014;32(21):2240–7.
11. Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the tree study. J Clin Oncol. 2008;26(21):3523–9.
12. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase iii trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (folfoxiri) compared with infusional fluorouracil, leucovorin, and irinotecan (folfiri) as first-line treatment for metastatic colorectal cancer: the gruppo oncologico nord ovest. J Clin Oncol. 2007;25(13):1670–6.
13. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase iii study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008;26(12):2006–12.
14. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18(16):2938–47.
15. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-folfox4 treatment and ras mutations in colorectal cancer. N Engl J Med. 2013;369(11):1023–34.
16. Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the bicc-c study. J Clin Oncol. 2007;25(30):4779–86.
17. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor kras and braf mutation status. J Clin Oncol. 2011;29(15):2011–9.
18. Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, et al. A randomized phase iiib trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009;27(5):672–80.
19. Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360(6):563–72.
20. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359(17):1757–65.
21. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type kras is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(10):1626–34.
22. Atreya CE, Corcoran RB, Kopetz S. Expanded ras: refining the patient population. J Clin Oncol. 2015;33(7):682–5.
23. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Final results from prime: randomized phase iii study of panitumumab with folfox4 for first-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25(7):1346–55.
24. Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, et al. Wild-type braf is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26(35):5705–12.
25. Kim G, McKee AE, Ning YM, Hazarika M, Theoret M, Johnson JR, Xu QC, Tang S, Sridhara R, Jiang X, He K, Roscoe D, McGuinn WD, Helms WS, Russell AM, Miksinski SP, Zirkelbach JF, Earp J, Liu Q, Ibrahim A, Justice R, Pazdur R. FDA approval summary: vemurafenib for treatment of unresectable or metastatic melanoma with the BRAFV600E mutation. Clin Cancer Res. 2014;20(19):4994–5000.
26. Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, et al. Vemurafenib in multiple nonmelanoma cancers with braf v600 mutations. N Engl J Med. 2015;373(8):726–36.
27. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to pd-1 blockade. Science. 2017;357(6349):409–13.
28. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (checkmate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017;18(9):1182–91.
29. Bertotti A, Papp E, Jones S, Adleff V, Anagnostou V, Lupo B, et al. The genomic landscape of response to egfr blockade in colorectal cancer. Nature. 2015;526(7572):263–7.
30. National Comprehensive Cancer Network. Nccn guidelines version 1.2016 colon cancer. 2015 [November 15, 2015]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
31. Brule SY, Jonker DJ, Karapetis CS, O'Callaghan CJ, Moore MJ, Wong R, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in ncic co.17. Eur J Cancer. 2015;51(11):1405–14.
32. Schrag D, Weng S, Brooks G, Meyerhardt JA, Venook AP. The relationship between primary tumor sidedness and prognosis in colorectal cancer. J Clin Oncol. 2016;34(15_suppl):3505.
33. Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, et al. Prognostic and predictive relevance of primary tumor location in patients with ras wild-type metastatic colorectal cancer: retrospective analyses of the crystal and fire-3 trials. JAMA Oncol. 2016.
34. Venook AP, Niedzwiecki D, Innocenti F, Fruth B, Greene C, O'Neil BH, Shaw JE, Atkins JN, Horvath LE, Polite BN, Meyerhardt JA, O'Reilly EM, Goldberg RM, Hochster HS, Blanke CD, Schilsky RL, Mayer RJ, Bertagnolli MM, Lenz H-J. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol. 2016;34(15_suppl):3504.
35. Salem ME, Lenz H-J, Xiu J, Hwang JJ, Philip PA, Shields AF, et al. Colorectal cancer: impact of primary tumor location on genetic alterations. J Clin Oncol. 2017;35(15_suppl):3578.
36. Andre T, Bensmaine MA, Louvet C, Francois E, Lucas V, Desseigne F, et al. Multicenter phase ii study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. J Clin Oncol. 1999;17(11):3560–8.
37. Cheeseman SL, Joel SP, Chester JD, Wilson G, Dent JT, Richards FJ, et al. A 'modified de gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer. 2002;87(4):393–9.
38. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009;27(5):663–71.
39. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. Folfiri followed by folfox6 or the reverse sequence in advanced colorectal cancer: a randomized gercor study. J Clin Oncol. 2004;22(2):229–37.

40. Reidy DL, Chung KY, Timoney JP, Park VJ, Hollywood E, Sklarin NT, et al. Bevacizumab 5 mg/kg can be infused safely over 10 minutes. J Clin Oncol. 2007;25(19):2691–5.
41. Ye LC, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with kras wild-type unresectable colorectal liver-limited metastases. J Clin Oncol. 2013;31(16):1931–8.
42. Tabernero J, Ciardiello F, Rivera F, Rodriguez-Braun E, Ramos FJ, Martinelli E, et al. Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase i dose-escalation study. Ann Oncol. 2010;21(7):1537–45.
43. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer. 1998;34(8):1274–81.
44. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage iii colon cancer. J Clin Oncol. 2011;29(11):1465–71.
45. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan study group. N Engl J Med. 2000;343(13):905–14.
46. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42.
47. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Final results from a randomized phase 3 study of folfiri {+/−} panitumumab for second-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25(1):107–16.
48. Patt YZ, Lee FC, Liebmann JE, Diamandidis D, Eckhardt SG, Javle M, et al. Capecitabine plus 3-weekly irinotecan (xeliri regimen) as first-line chemotherapy for metastatic colorectal cancer: phase ii trial results. Am J Clin Oncol. 2007;30(4):350–7.
49. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the bicc-c study. J Clin Oncol. 2008;26(4):689–90.
50. Venook AP, Niedzwiecki D, Lenz H, Innocenti F, Mahoney MR, O'Neil BH, et al. Calgb/swog 80405: phase iii trial of irinotecan/5-fu/leucovorin (folfiri) or oxaliplatin/5-fu/leucovorin (mfolfox6) with bevacizumab (bv) or cetuximab (cet) for patients (pts) with kras wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (mcrc). J Clin Oncol. 2014;32(5s):abstr LBA3.
51. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al. Initial therapy with folfoxiri and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014;371(17):1609–18.
52. Minagawa M, Yamamoto J, Miwa S, Sakamoto Y, Kokudo N, Kosuge T, et al. Selection criteria for simultaneous resection in patients with synchronous liver metastasis. Arch Surg. 2006;141(10):1006–12; discussion 1013.
53. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, et al. Liver resection for colorectal metastases. J Clin Oncol. 1997;15(3):938–46.
54. Reddy SK, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, Barbas AS, Abdalla EK, Choti MA, Vauthey J-N, Ludwig KA, Mantyh CR, Morse MA, Clary BM. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol. 2007;14(12):3481–91.
55. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative folfox4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (eortc 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14(12):1208–15.
56. Suzuki H, Kiyoshima M, Kitahara M, Asato Y, Amemiya R. Long-term outcomes after surgical resection of pulmonary metastases from colorectal cancer. Ann Thorac Surg. 2015;99(2):435–40.
57. Folprecht G, Gruenberger T, Bechstein W, Raab HR, Weitz J, Lordick F, et al. Survival of patients with initially unresectable colorectal liver metastases treated with folfox/cetuximab or folfiri/cetuximab in a multidisciplinary concept (celim study). Ann Oncol. 2014;25(5):1018–25.
58. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the celim randomised phase 2 trial. Lancet Oncol. 2010;11(1):38–47.
59. Gruenberger T, Bridgewater J, Chau I, Garcia Alfonso P, Rivoire M, Mudan S, et al. Bevacizumab plus mfolfox-6 or folfoxiri in patients with initially unresectable liver metastases from colorectal cancer: the olivia multinational randomised phase ii trial. Ann Oncol. 2015;26(4):702–8.
60. Huiskens J, van Gulik TM, van Lienden KP, Engelbrecht MR, Meijer GA, van Grieken NC, et al. Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, a study protocol of the randomised phase 3 cairo5 study of the dutch colorectal cancer group (dccg). BMC Cancer. 2015;15:365.
61. Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: Ffcd achbth aurc 9002 trial. J Clin Oncol. 2006;24(31):4976–82.
62. Ychou M, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, et al. A randomized phase iii study comparing adjuvant 5-fluorouracil/folinic acid with folfiri in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol. 2009;20(12):1964–70.
63. Kemeny N, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med. 1999;341(27):2039–48.
64. Sirtex. Sir-spheres microspheres package insert. http://www.sirtex.com/media/29845/ssl-us-10.pdf2014 [cited 2015 November 29].
65. van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, et al. Sirflox: randomized phase iii trial comparing first-line mfolfox6 (plus or minus bevacizumab) versus mfolfox6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol. 2016;34(15):1723–31.
66. Wasan HS, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (foxfire, sirflox, and foxfire-global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017;18(9):1159–71.
67. Hubbard JM, Grothey A. When less is more: maintenance therapy in colorectal cancer. Lancet (London, England). 2015;385(9980):1808–10.
68. Kasi PM, Grothey A. Chemotherapy maintenance. Cancer J (Sudbury, Mass). 2016;22(3):199–204.
69. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, et al. Optimox1: a randomized study of folfox4 or folfox7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer–a gercor study. J Clin Oncol. 2006;24(3):394–400.
70. Chibaudel B, Maindrault-Goebel F, Lledo G, Mineur L, Andre T, Bennamoun M, et al. Can chemotherapy be discontinued in unre-

sectable metastatic colorectal cancer? The gercor optimox2 study. J Clin Oncol. 2009;27(34):5727–33.
71. Labianca R, Sobrero A, Isa L, Cortesi E, Barni S, Nicolella D, Aglietta M, Lonardi S, Corsi D, Turci D, Beretta GD, Fornarini G, Dapretto E, Floriani I, Zaniboni A, Italian Group for the Study of Gastrointestinal Cancer-GISCAD. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. Ann Oncol. 2011;22(5):1236–42. https://doi.org/10.1093/annonc/mdq580. Epub 2010 Nov 15. PubMed PMID: 21078826.
72. Diaz-Rubio E, Pietrantonio F, de Braud F. Continuing single-agent bevacizumab as maintenance therapy after induction xelox (or folfox) plus bevacizumab in first-line treatment of metastatic colorectal cancer. Oncologist. 2012;17(11):1426–8.
73. Koeberle D, Betticher DC, von Moos R, Dietrich D, Brauchli P, Baertschi D, et al. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase iii non-inferiority trial (sakk 41/06). Ann Oncol. 2015;26(4):709–14.
74. Simkens LH, van Tinteren H, May A, ten Tije AJ, Creemers GJ, Loosveld OJ, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (cairo3): a phase 3 randomised controlled trial of the dutch colorectal cancer group. Lancet (London, England). 2015;385(9980):1843–52.
75. Hegewisch-Becker S, Graeven U, Lerchenmuller CA, Killing B, Depenbusch R, Steffens CC, et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (aio 0207): a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol. 2015;16(13):1355–69.
76. Tournigand C, Chibaudel B, Samson B, Scheithauer W, Vernerey D, Mesange P, et al. Bevacizumab with or without erlotinib as maintenance therapy in patients with metastatic colorectal cancer (gercor dream; optimox3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2015;16(15):1493–505.
77. Alfonso PG, Benavides M, Ruiz AS, Guillen-Ponce C, Safont MJ, Alcaide J, et al. 499ophase ii study of first-line mfolfox plus cetuximab (c) for 8 cycles followed by mfolfox plus c or single agent (s/a) c as maintenance therapy in patients (p) with metastatic colorectal cancer (mcrc): the macro-2 trial (spanish cooperative group for the treatment of digestive tumors [ttd]). Ann Oncol. 2014;25(suppl 4):iv168.
78. Tveit KM, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, et al. Phase iii trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (nordic flox) versus flox alone in first-line treatment of metastatic colorectal cancer: the nordic-vii study. J Clin Oncol. 2012;30(15):1755–62.
79. Pfeiffer P, Sorbye H, Qvortrup C, Karlberg M, Kersten C, Vistisen K, et al. Maintenance therapy with cetuximab every second week in the first-line treatment of metastatic colorectal cancer: the nordic-7.5 study by the nordic colorectal cancer biomodulation group. Clin Colorectal Cancer. 2015;14(3):170–6.
80. Wasan H, Meade AM, Adams R, Wilson R, Pugh C, Fisher D, et al. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with kras wild-type advanced colorectal cancer (coin-b): a randomised phase 2 trial. Lancet Oncol. 2014;15(6):631–9.
81. Chibaudel B, Tournigand C, Bonnetain F, Maindrault-Goebel F, Lledo G, Andre T, et al. Platinum-sensitivity in metastatic colorectal cancer: towards a definition. Eur J Cancer. 2013;49(18):3813–20.
82. de Gramont A. Re-challenge and the concept of lines of therapy in metastatic colorectal cancer. Eur J Cancer. 2011;47(Suppl 3):S76–84.
83. Townsley CA, Major P, Siu LL, Dancey J, Chen E, Pond GR, et al. Phase ii study of erlotinib (osi-774) in patients with metastatic colorectal cancer. Br J Cancer. 2006;94(8):1136–43.
84. Mesange P, Poindessous V, Sabbah M, Escargueil AE, de Gramont A, Larsen AK. Intrinsic bevacizumab resistance is associated with prolonged activation of autocrine vegf signaling and hypoxia tolerance in colorectal cancer cells and can be overcome by nintedanib, a small molecule angiokinase inhibitor. Oncotarget. 2014;5(13):4709–21.
85. Bennouna J, Sastre J, Arnold D, Osterlund P, Greil R, Van Cutsem E, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ml18147): a randomised phase 3 trial. Lancet Oncol. 2013;14(1):29–37.
86. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausova J, Macarulla T, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase iii randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30(28):3499–506.
87. Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, et al. Ramucirumab versus placebo in combination with second-line folfiri in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (raise): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015;16(5):499–508.
88. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004;351(4):337–45.
89. Saltz LB, Lenz HJ, Kindler HL, Hochster HS, Wadler S, Hoff PM, et al. Randomized phase ii trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the bond-2 study. J Clin Oncol. 2007;25(29):4557–61.
90. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007;357(20):2040–8.
91. Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, et al. Epic: phase iii trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(14):2311–9.
92. Middleton G, Brown S, Lowe C, Maughan T, Gwyther S, Oliver A, et al. A randomised phase iii trial of the pharmacokinetic biomodulation of irinotecan using oral ciclosporin in advanced colorectal cancer: results of the panitumumab, irinotecan & ciclosporin in colorectal cancer therapy trial (piccolo). Eur J Cancer. 2013;49(16):3507–16.
93. Seymour MT, Brown SR, Middleton G, Maughan T, Richman S, Gwyther S, et al. Panitumumab and irinotecan versus irinotecan alone for patients with kras wild-type, fluorouracil-resistant advanced colorectal cancer (piccolo): a prospectively stratified randomised trial. Lancet Oncol. 2013;14(8):749–59.
94. Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, Firn JI, Paice JA, Peppercorn JM, Phillips T, Stovall EL, Zimmermann C, Smith TJ. Integration of palliative care into standard oncology care: american society of clinical oncology clinical practice guideline update. J Clin Oncol. 2017;35(1):96–112.
95. Bottomley A. The cancer patient and quality of life. Oncologist. 2002;7(2):120–5.
96. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase iii trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25(13):1658–64.
97. Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type kras exon 2 metastatic colorectal cancer

(aspecct): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol. 2014;15(6):569–79.
98. Kim JH. Chemotherapy for colorectal cancer in the elderly. World J Gastroenterol. 2015;21(17):5158–66.
99. Foubert F, Matysiak-Budnik T, Touchefeu Y. Options for metastatic colorectal cancer beyond the second line of treatment. Dig Liver Dis. 2014;46(2):105–12.
100. Abou-Elkacem L, Arns S, Brix G, Gremse F, Zopf D, Kiessling F, et al. Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. Mol Cancer Ther. 2013;12(7):1322–31.
101. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (correct): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet (London, England). 2013;381(9863):303–12.
102. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, Xu J, Bai Y, Chi Y, Wang L, Yeh KH, Bi F, Cheng Y, Le AT LJK, Liu T, Ma D, Kappeler C, Kalmus J, Kim TW, CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2015;16(6):619–29. https://doi.org/10.1016/S1470-2045(15)70156-7. Epub 2015 May 13. PubMed PMID: 25981818.
103. Goldstein DA, Ahmad BB, Chen Q, Ayer T, Howard DH, Lipscomb J, et al. Cost-effectiveness analysis of regorafenib for metastatic colorectal cancer. J Clin Oncol. 2015;33(32):3727–32.
104. Heidelberger C, Parsons DG, Remy DC. Syntheses of 5-trifluoromethyluracil and 5-trifluoromethyl-2′-deoxyuridine. J Med Chem. 1964;7:1–5.
105. Peters GJ. Therapeutic potential of tas-102 in the treatment of gastrointestinal malignancies. Ther Adv Med Oncol. 2015;7(6):340–56.
106. Lenz HJ, Stintzing S, Loupakis F. Tas-102, a novel antitumor agent: a review of the mechanism of action. Cancer Treat Rev. 2015;41(9):777–83.
107. Rahman L, Voeller D, Rahman M, Lipkowitz S, Allegra C, Barrett JC, et al. Thymidylate synthase as an oncogene: a novel role for an essential DNA synthesis enzyme. Cancer Cell. 2004;5(4):341–51.
108. Temmink OH, Emura T, de Bruin M, Fukushima M, Peters GJ. Therapeutic potential of the dual-targeted tas-102 formulation in the treatment of gastrointestinal malignancies. Cancer Sci. 2007;98(6):779–89.
109. Fukushima M, Suzuki N, Emura T, Yano S, Kazuno H, Tada Y, et al. Structure and activity of specific inhibitors of thymidine phosphorylase to potentiate the function of antitumor 2′-deoxyribonucleosides. Biochem Pharmacol. 2000;59(10):1227–36.
110. Bendell JC, Rosen LS, Mayer RJ, Goldman JW, Infante JR, Benedetti F, et al. Phase 1 study of oral tas-102 in patients with refractory metastatic colorectal cancer. Cancer Chemother Pharmacol. 2015;76(5):925–32.
111. Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, et al. Tas-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 2012;13(10):993–1001.
112. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of tas-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909–19.
113. Singh PP, Sharma PK, Krishnan G, Lockhart AC. Immune checkpoints and immunotherapy for colorectal cancer. Gastroenterol Rep (Oxf). 2015;3(4):289–97.
114. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–20. https://doi.org/10.1056/NEJMoa1500596.
115. McCain J. The mapk (erk) pathway: Investigational combinations for the treatment of braf-mutated metastatic melanoma. P T. 2013;38(2):96–108.
116. Kopetz S, Desai J, Chan E, Hecht JR, O'Dwyer PJ, Maru D, et al. Phase ii pilot study of vemurafenib in patients with metastatic braf-mutated colorectal cancer. J Clin Oncol. 2015;33(34):4032–8.
117. Mesteri I, Bayer G, Meyer J, Capper D, Schoppmann SF, von Deimling A, et al. Improved molecular classification of serrated lesions of the colon by immunohistochemical detection of braf v600e. Mod Pathol. 2014;27(1):135–44.
118. Tran B, Kopetz S, Tie J, Gibbs P, Jiang ZQ, Lieu CH, et al. Impact of braf mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer. 2011;117(20):4623–32.
119. Pietrantonio F, Petrelli F, Coinu A, Di Bartolomeo M, Borgonovo K, Maggi C, et al. Predictive role of braf mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J Cancer. 2015;51(5):587–94.
120. Corcoran RB, Dias-Santagata D, Bergethon K, Iafrate AJ, Settleman J, Engelman JA. Braf gene amplification can promote acquired resistance to mek inhibitors in cancer cells harboring the braf v600e mutation. Sci Signal. 2010;3(149):ra84.
121. Kopetz S, McDonough SL, Morris VK, Lenz H-J, Magliocco AM, Atreya CE, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in braf-mutant metastatic colorectal cancer (swog 1406). J Clin Oncol. 2017;35(4_suppl):520.
122. Leto SM, Trusolino L. Primary and acquired resistance to egfr-targeted therapies in colorectal cancer: impact on future treatment strategies. J Mol Med (Berlin, Germany). 2014;92(7):709–22.
123. Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (her2) in cancers: overexpression and therapeutic implications. Mol Biol Int. 2014;2014:852748.
124. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;4:CD006243.
125. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of her2-positive advanced gastric or gastro-oesophageal junction cancer (toga): a phase 3, open-label, randomised controlled trial. Lancet (London, England). 2010;376(9742):687–97.
126. Seo AN, Kwak Y, Kim DW, Kang SB, Choe G, Kim WH, et al. Her2 status in colorectal cancer: its clinical significance and the relationship between her2 gene amplification and expression. PLoS One. 2014;9(5):e98528.
127. Siena S, Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, et al. Therapeutic dual inhibition of her2 pathway for metastatic colorectal cancer (mcrc): the heracles trial. ASCO Meet Abstr. 2015;33(3_suppl):565.
128. Sartore-Bianchi A, Marsoni S, Trusolino L, Martino C, Lonardi S, Leone F, et al. D26pertuzumab and trastuzumab-emtansine in her2 positive metastatic colorectal cancer: the heracles b trial. Ann Oncol. 2016;27(suppl_4):iv47.

Treatment of Rectal Cancer

9

Mehmet Artaç, Bassel F. El-Rayes, Suayib Yalcin, and Philip A. Philip

Introduction

The incidence of colorectal cancer (CRC) is increasing, especially in patients younger than 50 years. The reason for this increase remains unknown at this time. Rectal cancer (RC) represents approximately 30% of all CRC [1]. In the last two decades, new multimodality strategies have reduced the local recurrence (LR) rate and extended the duration of overall survival (OS) [2]. The mainstay of treatment remains surgery [3]; however, downsizing the tumor by neoadjuvant treatment and adjuvant therapy for systemic disease has shown significant additional benefit. The standardization of total mesorectal excision (TME), radiation treatment (RT) dose delivery, optimal timing, and sequencing of treatment modalities with the use of prolonged administration of a fluoropyrimidine concurrent with RT have significantly decreased the rates of LR in the patients with locally advanced rectal cancer (LARC) [4].

Risk assessment with magnetic resonance imaging (MRI) and/or endoscopic ultrasound (EUS) must be undertaken prior to surgery in patients with non-metastatic disease to accurately plan multimodality therapy [5]. Molecular analysis of rectal tumor is expected to play an increasing role in individualized treatment plans [6].

LR after the treatment of RC was previously seen in more than 30% of patients and was associated with a worse outcome [7]. LR rates dropped to less than 5% with the improvement in surgical techniques and routine incorporation of preoperative therapies. Furthermore, some recent studies support the notion that survival of RC patients is better than those with colon cancer – possibly a result of improvements in the use of multimodality therapy [8]. Nevertheless, the impact of RT or CRT on survival or reduction of distant metastases was not demonstrated [9, 10]. The incorporation of newer agents in chemoradiation (CRT) regimens has increased toxicity with modest or no increase in disease control [11–13].

In patients who have undergone radical surgery, decisions regarding adjuvant therapy must be dictated by the stage at presentation [14]. Adjuvant chemotherapy or stage II RC is not routinely recommended similar to stage II colon cancers. However, for selected stage II RC patients – including inadequately sampled lymph nodes, T4 lesions, perforation, or poorly differentiated histology – adjuvant therapy should be considered [15].

Short-course radiotherapy (SCRT) with immediate surgery or long-course radiotherapy (LCRT) plus chemotherapy with delayed surgery are the most frequently used RT regimens in RC. SCRT preoperatively for stage II or III patients are reasonable options if no tumor downsizing is needed. Nevertheless, there are some concerns regarding side effects to RT resulting from high-dose-per-fraction [16].

Staging of Rectal Cancer

Extramural depth of tumor invasion in RC is prognostically important and determines the pre-and postoperative treatment decisions. A meta-analysis of 90 studies indicated that MRI and EUS have similar sensitivity in the evaluation of

M. Artaç
Department of Medical Oncology, Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey

B. F. El-Rayes (✉)
Clinical Research, Department of Hematology and Medical Oncology, Emory University School of Medicine/Winship Cancer Institute of Emory University, Atlanta, GA, USA
e-mail: bassel.el-rayes@emoryhealthcare.org

S. Yalcin
Department of Internal Medicine, Division of Medical Oncology, Hacettepe University School of Medicine, Institute of Cancer, Altındağ, Ankara, Turkey

P. A. Philip
Department of Oncology, Department of Pharmacology, Wayne State University, Karmanos Cancer Institute, Hudson-Webber Cancer Research Center, Detroit, MI, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_9

the depth of tumor penetration through the muscularis propria (94%). EUS was more specific for evaluating local tumor invasion (86% vs. 69%) [17]. Suzuki et al. demonstrated the importance of MRI for the evaluation of adjacent organ status in locally advanced rectal cancer [18]. MRI is now a standard practice in many European countries. Experts agree that EUS and high-resolution MRI are established methods to determine preoperative local tumor (T) stage. The maximal extramural depth (EMD) of tumor spread, defined as the distance from the outer edge of the longitudinal muscularis propria to the outer edge of the tumor, was measured in the MERCURY trial [19]. The MR and histopathology results were considered to be equal to each other (95% confidence interval [1] of the difference was within ±0.5 mm). The MERCURY study showed that it was feasible to determine prognosis with true measurement of the depth of extramural tumor spread by thin-section MR. As a result, RC can be categorized into three prognostic subgroups with MRI-based staging according to the predicted relationship of the tumor to the circumferential resection margin (CRM), the degree of extramural spread, lymph node status, and the presence of extramural venous invasion. The tumors were classified as low (0–5 cm), medium (5.1–10 cm), and high (10.1–15 cm), according to the distance between the distal end of the tumor and the anorectal junction as measured by MRI [19].

Optimal Surgical Approach

The definitive therapy for RC remains surgical resection by total mesorectal excision in the vast majority of patients especially those with no metastatic disease [20, 21]. Rates of recurrence with surgery alone were more than 50% before TME [22, 23]. LR rates after surgery significantly decreased with the widespread adoption of TME compared to older surgical techniques. The American Joint Committee on Cancer (AJCC) recommends the evaluation of 12 lymph nodes to accurately identify early stage colorectal cancers [24]. The rate of CRM positivity is 5% or less with TME by low anterior resection versus 10% and 25% for abdominoperineal resection. As expected, there is a higher LR rate with the abdominoperineal approach. There is evidence to support that a CRM of 1 mm or less may adversely affect survival, due to increased likelihood of LR and distant metastases [25]. Despite the low rates of LR after TME even without the use of any adjuvant treatment [26], LR risks could be further reduced by limiting surgeries to be performed by specially trained and certified surgeons [27].

Laparoscopic low anterior resection with TME is a new minimally invasive technique in colorectal surgery. Several randomized controlled trials that compared the oncological outcomes of open and laparoscopic surgery for rectal cancers were conducted [20]. These trials showed several advantages related to minimally invasive surgery with noninferior oncological long-term outcomes between open and laparoscopic surgeries [28–30]. These advantages are: less postoperative pain and decreased hospital stay and recovery time. According to the COLOR II trial, laparoscopic surgery in patients with rectal cancer was associated with rates of locoregional recurrence and disease-free and overall survival similar to those for open surgery [31]. The most recent ACOSOG Z6051 and ALaCaRT trials had a primary end point definition focused on CRM, distal resection margin (DRM), and the completeness of the TME [32, 33]. Both of the trials failed to show noninferiority of laparoscopic low anterior resection compared to the effectiveness of open surgery.

Robotic platform is another new minimally invasive treatment of rectal cancer. The ROLARR trial failed to demonstrate any significant difference in the conversion rate to open surgery between robotic and laparoscopic resection [34]. TME quality, CRM involvement, and 30-day morbidity were not different between these techniques.

The transanal minilaparoscopy-assisted natural orifice transluminal endoscopic surgery (NOTES) approach holds significant promise as a safe and less morbid alternative to conventional low anterior rectal resection [35]. NOTES reduces the trauma associated with conventional surgery by maintaining the integrity of the abdominal wall. Transanal TME may represent an innovation for the treatment of rectal cancer, particularly cancers in the middle and distal parts of the rectum. Transanal TME improves the quality of the resection when compared with laparoscopic surgery, by allowing longer DRM and optimal CRM with adequate lymph node dissection, notably for male patients with a narrow pelvis, a bulky mesorectum, or visceral obesity [20]. However, transanal TME is a novel technique, and the data are derived only from observational studies. Standardization of the surgical procedure is important before any generalization can be made on this technique. The results of the ongoing COLOR III trial, which compares transanal TME with laparoscopic TME, will be important for the standardization of these surgical procedures in rectal cancer [36].

Preoperative Radiotherapy

Treatment of RC with surgery alone, with neoadjuvant [37–42] or adjuvant [43–46] RT were explored in many studies. Preoperative RT was suggested to be more effective than postoperative RT in lowering LR rates [47, 48]. In the first Stockholm trial evaluating preoperative SCRT (SCRT technique from Siegel et al. [49]) in operable RC patients who received RT, the relative reduction in the LR rate was greater than 50% after 5 years [50]. However, the postoperative mortality within 30 days of surgery was increased after RT,

Table 9.1 Surgery with or without RT

Study/published date/reference	No	LR rate %	DFS rate %	OS rate %	Median follow-up time (months)
Dutch TME trial/2010 [53]					
Surgery alone	704	11	–	No difference	
Surgery + preoperative SCRT	713	4.6			
Stocholm II/1996 [51]					
Surgery alone	285	25	–	39	106
Surgery + preoperative SCRT	272	12		46	
		$p < 0.001$		$p < 0.03$	
Kapiteijn et al./2001 [52]					
Surgery alone	875	8.2	79.1	81.8	24.9
Surgery + preoperative SCRT	873	2.4	83.9	82	
		$p < 0.001$	$p = 0.09$	$p = 0.84$	
Swedish Rectal Cancer Trial/2009 [55]					
Surgery alone	557	27	62	48	75
Surgery + preoperative SCRT	553	11	72	58	
		$p < 0.001$	$p < 0.001$	$p = 0.004$	

SCRT Short-course radiotherapy, *LCRT* long-course radiotherapy, *LR* local recurrence, *DFS* disease-free survival, *OS* overall survival, *No* number of patients in each group, *RT* radiotherapy

mainly in older patients. In the Stockholm II trial, patients were randomized to preoperative SCRT followed by surgery within a week or surgery alone [51]. With a median follow-up of 8.8 years and in patients who underwent curative surgery the incidence of pelvic recurrence was 12% and 25% in SCRT versus no SCRT groups, respectively ($p < 0.001$). The overall survival (OS) rate in the irradiated patients who underwent curative surgery was also improved (46% versus 39%, $p < 0.03$). Kapiteijn et al. evaluated the efficacy of preoperative SCRT combined with standardized TME in patients with resectable RC [52]. The rates of LR at 2 years were 2.4% in the group assigned to RT before surgery and 8.2% in the group in which the patients received surgery alone ($p < 0.001$) The overall rate of LR at 2 years was 16.1% in the group assigned to RT and surgery and 20.9% in the group assigned to surgery alone ($p = 0.09$). Preoperative SCRT reduced the risk of LR and improved local control of disease in the patients with RC who underwent a standardized TME.

A Dutch study randomized RC patients to TME alone versus preoperative SCRT followed by TME [53]. The 5-year LR rate was 4.6% in the RT + TME group and 11.0% in the TME-only group. TME reduced the risk of pelvic recurrence and favorably affected the survival after surgery. In this study, the recurrence area also was evaluated to show prognosis. Presacral LR is the most common type of LR and has a poor prognosis in general. Anastomotic and anterior recurrences have a relatively good prognosis. Lateral site LRs were seen in 20% of patients and the results were similar with the literature [54].

In the Swedish Rectal Cancer Trial preoperative SCRT (25 Gy/5 fractions) not only lowered the rate of LRs but also improved the overall survival. At 5 years, the LR rate was 11% in the SCRT group (vs. 27% in control group, $p < 0.001$). Patients who received SCRT had a better OS rate by 58% compared to surgery alone at 5 years (48%, $p < 0.004$). In this trial, the proportional reduction in the rates of LR was similar in all stages [55]. This has also been reported from the Stockholm trial [50]. Nevertheless, in patients with an anatomically very low tumor – particularly in men in whom an abdominoperineal excision is considered – preoperative RT should be considered irrespective of tumor stage, because such patients are at a high risk for local failure even if surgery is optimal.

The choice of patients with resectable RC who should receive preoperative RT must be individualized. Some surgeons are of the opinion that they can achieve very low rates of LR and good survival without preoperative RT, provided that the surgical technique is optimal [56]. However, preoperative RT improves local control in RC in almost all studies [51–53, 55] (Table 9.1). In two studies, Kapiteijn et al. [52] and Dutch [53], there was no advantage for OS compared to the Swedish and Stockholm trials.

Preoperative Versus Postoperative Concurrent Chemoradiotherapy

Choosing a postoperative or preoperative multi-modal treatment strategy in a given patient is an important consideration. The concurrent use of postoperative RT and 5-fluorouracil (5-FU) has been shown to reduce LRs and to improve survival in patients with LARC [57, 58]. The most definitive study comparing preoperative versus postoperative CRT was the German CAO/ARO/AIO-94 trial [59]. In this study, all patients underwent TME and received four cycles of chemotherapy postoperatively. This study randomly assigned patients with clinical stage T3 or T4 or node-

positive disease to receive either preoperative or postoperative CRT. Compared to postoperative CRT, the preoperative approach was superior in terms of treatment compliance, downsizing, acute and chronic toxicities, and 5-year local control rate [60]. Sphincter preservation was increased in the subgroup of patients who were thought to need an abdominoperineal resection (39% for preoperative CRT and 19% for postoperative CRT) when evaluated initially. The 10-year OS rates were 59.6% for preoperative CRT and 59.9% for postoperative CRT ($p = 0.85$). The 10-year cumulative incidence of LR was 7.1% for patients assigned to the preoperative CRT and 10.1% for patients in the postoperative CRT group ($p = 0.048$). There was a reduction in the late anastomotic strictures with preoperative therapy, and acute toxicity was also reduced by using preoperative CRT, both statistically significant. This study provided strong evidence of the advantages for preoperative CRT and increased possibility of sphincter preservation with the use of preoperative CRT. However, preoperative CRT did not improve survival over postoperative CRT.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial [61], surgery was performed within 8 weeks after RT completion. In the postoperative group, CT was started within 4 weeks after surgery. Preoperative CRT, compared with postoperative CRT, significantly improved disease-free survival (DFS); 5-year disease-free survival rates for preoperative and postoperative CRT patients were 64.7% and 53.4%, respectively ($p = 0.011$). Similar to the German CAO/ARO/AIO-94 trial [59], there was no significant difference in OS between the arms; the 5-year OS rates for preoperative and postoperative patients were 74.5% and 65.6%, respectively ($p = 0.065$). Unlike the German trial that demonstrated a significant reduction in the 5-year cumulative LR rate with preoperative CRT, there was no difference between preoperative or postoperative CRT arms in terms of LR in the NSABP R-03 trial. The difference of outcome in LR recurrence between the two studies could be influenced by the type and quality of the surgical procedure. It is noteworthy that not every single patient in the NSABP R-03 underwent a TME, compared with 100% of the patients in the German CAO/ARO/AIO-94 trial. The LR rates in the preoperative RT group were also lower in the Dutch trial [53], different from NSABPR-03 [61] in which each recurrence rate of the arms was equal to 10.7% at 5 years. The rate of LR at 2 years was reduced from 8.2% to 2.4% with the addition of preoperative RT. The difference in the LR rates between the Dutch and NSABP R-03 trials was due to the length of follow-up (2 vs. 5 years, respectively), dose of RT (25 vs. 50.4 Gy, respectively), timing of RT (5 days vs. 5 weeks, respectively), type of surgery (mandatory TME in the Dutch trial), and patient eligibility (inclusion of stage I patients in the Dutch study). Equivalent rates of LR between preoperative and postoperative therapy in the NSABP R-03 trial are difficult to explain because there were only 28 locoregional events observed in this trial, and the statistical power to detect a 33% reduction in LR was only 18% (see Table 9.2) [43, 59, 61–66].

Another group of studies addressed optimal postoperative treatment (Table 9.2) [43, 59, 61–66]. NSABP R-02 randomized Dukes' B or C rectal cancer patients [65] to either postoperative CT alone or CT and postoperative RT. The latter resulted in no improvement in DFS ($p = 0.90$) or OS ($p = 0.89$), but it decreased the cumulative incidence of LR from 13% to 8% at 5-year follow-up ($p = 0.02$). The results were similar to the previously reported findings from NSABP R-01 [43]. The CT group, when compared with the surgery alone group, showed an overall increase in DFS ($p = 0.006$) and OS ($p = 0.05$). There was a decrease in LR from 25% to 16% with postoperative radiation compared to surgery alone ($p = 0.06$). No significant benefit in overall DFS ($p = 0.4$) or survival ($p = 0.7$) from the use of radiation was demonstrated. The conclusion from these studies was that adjuvant CT is beneficial in the management of RC. Postoperative RT, administered alone or together with CT, is unsuccessful in changing the subsequent incidence of distant disease. This will be in contrast to the conclusions from the GITSG 7175 trial [64]. In GITSG 7175 trial, receiving CT after surgery significantly reduced the LR and demonstrated an increase in DFS rates independently from the use of RT, resulting in a discrepancy of outcome when we compare with the NSABP R-02 study [65]. In the GITSG 7175 trial there was no postoperative CT alone arm. It is possible that the significant prolongation of DFS was because of CT. This assertion was strengthened by the NSABP R-01 results, which concluded that CT, not concurrent with RT, achieved an increase in DFS and OS. Although the use of RT before surgery for low-lying lesions of the rectum has become more frequent to control LRs, survival advantage was detected to be only statistically significant in a few trials: the Stockholm II and Swedish studies [51, 53].

The COPERNICUS trial compared giving neoadjuvant chemotherapy prior to SCRT then surgery within a short time interval in operable RC, which proved feasible with good compliance and promising efficacy [67]. The FOWARC study reported preliminary results of the efficacy of FOLFOX6 (leucovorin calcium [folinic acid], fluorouracil, and oxaliplatin) concurrent with RT or FOLFOX6 alone in a neoadjuvant setting. FOLFOX6 concurrent with RT resulted in higher pCR (pathological complete response) rate, neoadjuvant FOLFOX6 alone achieved a similar downstaging rate with less toxicity and post-op complications, compared to preoperative 5-FU with RT [68].

Table 9.2 Neoadjuvant and adjuvant approaches in RC patients: CT, RT, CRT, and surgery

	Study/published date/reference	No	LR rate %	DFS rate %	OS rate %	Median follow-up time (months)
Addition CT to preoperative RT trials	Polish rectal trial/2006 [62]					
	Surgery + pre-op SCRT Surgery + pre-op LCRT + CT		9 14.2 $p = 0.170$	58.4 55.6 $p = 0.820$	67.2 66.2 $p = 0.960$	48
	TROG trial/2012 [63]					
	Surgery + pre-op SCRT Surgery + pre-op SCRT + CT	163 163	7.5 4.4 $p = 0.24$	27 30 $p = 0.92$	74 70 $p = 0.62$	71
Postoperative trials	GITSG/1988 [64]					
	Surgery alone Surgery + post-op RT Surgery + post-op CRT	58 50 46	43.1 40.0 21.7 $p = 0.005$	44 50 65 $p = 0.01$	–	
	NSABP-RO-1/1988 [43]					
	Surgery alone Surgery + post-op RT Surgery + post-op CT	179 182 183	25 16 [a] $p = 0.06$	30 [a] 42 $p = 0.006$	43 [a] 53 $p = 0.05$	64.1
	NSABP-RO-2/2000 [65]					
	Surgery + post-op CT Surgery + post-op CRT	348 346	13 8 $p = 0.02$	No significance $p = 0.9$	No significance $p = 0.89$	Average 93
Preoperative and postoperative	German CAO/ARO/AIO-94 trial/2012 [59]					
	Surgery + pre-op CRT Surgery + post-op CRT	404 395	7.1 10.1 $p = 0.048$	29.8 29.6 $p = 0.9$	59.6 59.9 $p = 0.85$	134
	NSABP-RO-3/2009 [61]					
	Surgery + pre-op CRT Surgery + post-op CRT	123 131	10.7 10.7 $p = 0.693$	64.7 53.4 $p = 0.011$	74.5 65.6 $p = 0.065$	101
	MRC and NCIC C016/2009 [66]					
	Surgery + pre-op SCRT Surgery + post-op CRT	674 676	4.7 11.5 $p < 0.0001$	73.6 66.7 $p = 0.013$	70.3 67.9 $p = 0.40$	48

SCRT Short-course radiotherapy, *LCRT* long-course radiotherapy, *LR* local recurrence, *DFS* disease-free survival, *OS* overall survival, *No* number of patients in each group, *CT* chemotherapy, *RT* radiotherapy
[a]There is not any difference with these rates

Optimal Delivery of Radiotherapy

Preoperative SCRT without concurrent chemotherapy is the preferred modality in some European countries. However, oncologists in the United States did not adopt this SCRT approach because of the potential for late radiation morbidity and anorectal dysfunction resulting from hypofractionation of the total radiation dose. In the United States, stage II or higher RC is more commonly treated with preoperative CRT consisting of 45–50.4 Gy of RT (over 5–6 weeks) concurrent with infusional 5-FU or oral capecitabine to be followed by surgery in 6–10 weeks after the completion of CRT.

The UK Medical Research Council (MRC) and the National Cancer Institute of Canada (NCIC) randomized patients to receive either preoperative SCRT (25 Gy in five fractions; $n = 674$) followed by surgery or surgery with selective postoperative CRT (45 Gy in 25 fractions with concurrent infusion 5-FU) [66]. LR rates were 10.6% in the postoperative CRT group and 4.4% in the preoperative SCRT group ($p < 0.0001$). But, there was no significant difference in the OS rates between the two arms of the study [66]. In the Swedish Rectal Cancer Trial, the LR rate was 11% in the SCRT group at 5 years (vs. 27% in the group treated with surgery alone $p < 0.001$). Interestingly, patients who received SCRT had a higher OS rate compared to sur-

gery alone (58% vs. 48%, $p < 0.004$) [55]. Also as mentioned before in some of the studies [51, 52, 69], their results supported the MRC CR07/NCIC-CTG C016 trial in terms of LR rates. The OS was not different in the MRC CR07/NCIC-CTG trial similarly with some studies NSABP-RO-3 [61], German CAO/ARO/AIO-94 [59]. In the Dutch trial [53], the 5-year LR rates were seen in 4.6% of the SCRT group and 11% of the surgery alone group ($p < 0.001$). OS was similar in both. The effect of SCRT on LR remained even after 12 years.

The results of all the trials confirm that neoadjuvant RT improves the LR rates. The optimal RT delivery remains in question with respect to LR and OS. In the Stockholm III trial [70], significantly more complications were seen in 24 of 37 (65%) patients who underwent surgery 11–17 days after the start of SCRT, than in 29 of 75 (39%) patients who underwent surgery less than 11 days after the start of SCRT ($p = 0.04$). Besides these studies, other trials, which were designed for a SCRT alone group and LCRT concurrent with CT group, could not find any difference regarding LR rates, DFS, and OS [62, 63]. Treatment approaches should be individualized. Here, treatment toxicity and the patient's preferences are important points to consider when choosing LCRT or SCRT.

CRT has demonstrated the effectiveness in most clinical trials. Clinically resectable patients (cT1-3Nx) were included in SCRT trials, whereas CRT trials allowed only stage II (T3–4) or stage III (node [N] positive) disease. In the Polish rectal trial [62], the 4-year OS was 67.2% in the SCRT alone group and 66.2% in the SCRT+CT group ($p = 0.960$). DFS was 58.4 versus 55.6%, respectively ($p = 0.820$). LR rates were 9% versus 14% in the short course and long course, respectively ($p = 0.170$). Acute radiation toxicity was higher in the CRT group (18.2 vs. 3.2%; $p < 0.001$). However, there were no differences in late toxicities. No beneficial effect on survival or local control was obtained by the neoadjuvant CRT. Ngan et al. reported the results of the Trans-Tasmanian Radiation Oncology Group (TROG) trial [63]. They reported no significant difference in local relapse (7.5% for short-course, compared to 4.4% for long course, $p = 0.24$) after 3 years of follow-up. Additionally, no difference was observed in 5-year distant recurrences, relapse-free survival, or OS. There was no difference noted in the rate of sphincter-sparing surgery. Grade 3 or 4 late toxicity, as reported at 3 years, was not different between the two groups in this trial, similar to the Polish trial [62].

According to our interpretation of all these study results, the trials so far indicate that SCRT or LCRT are both acceptable treatment options for selected stage II and III RC patients. If the preoperative radiotherapy is used to improve sphincter preservation, then the standard long-course radiation should be the better choice.

Choice of Systemic Therapy

Fluoropyrimidines

5-Fluorouracil (5-FU) has been used for many years in the treatment of colorectal cancer. The use of long-term continuous infusion became the preferred standard when combined with postoperative radiotherapy [71]. In this study, there was an advantage to the continuous infusion 5-FU compared with bolus 5-FU in terms of local control, DFS, and OS. The NSABP R-04 trial established that capecitabine is noninferior to infusional 5-FU when used concurrently with preoperative radiation [72]. Other studies did not support the addition of drugs such as oxaliplatin [73], irinotecan [74], bevacizumab [75], cetuximab [12], or panitumumab [76]. Hence a fluoropyrimidines with either capecitabine or continuous infusion 5-FU became the standard systemic therapy regimen during radiation therapy.

Oxaliplatin and Irinotecan

The main neoadjuvant treatment approach for patients with clinical stage II and III RC is a fluoropyrimidine-based chemotherapy concurrent with RT. A study of infusional versus bolus 5-FU demonstrated that infusional rather than bolus 5-FU administered concurrently with RT increased the likelihood of a pCR in patients with LARC [77]. Preoperative chemotherapeutics that would increase complete pathological response are still being investigated. Availability of newer cytotoxic agents and targeted agents created the potential treatment strategies to be tested in clinical trials testing the contributions of capecitabine, oxaliplatin, and irinotecan.

The phase III trial ACCORD 12/0405-Prodige 2 compared neoadjuvant RT plus capecitabine with dose-intensified RT plus capecitabine and oxaliplatin [13]. The oxaliplatin-containing group had a higher percentage of pCR (19.2% vs. 13.9%) that was not significant statistically ($p = 0.09$). The grade 3 or 4 toxicity rates were significantly higher in the oxaliplatin-containing group (25% vs. 11%; $p < 0.001$), without difference in sphincter-sparing surgery rates (75% vs. 78%). The NSABP-04 trial randomized patients with rectal cancer to infusional 5-FU and oral capecitabine, with or without the oxaliplatin [71]. No differences between pCR rates, sphincter preservation, or surgical-downsizing were observed between the capecitabine and 5-FU regimens whether or not oxaliplatin was added. Patients who received oxaliplatin had significantly higher rates of grade 3 and grade 4 acute toxicities (15.4% vs. 6.6%; $p < 0.001$). The STAR-01 trial also investigated the efficacy of oxaliplatin-5FU combination in LARC patients.

The rate of pCR was 16% in both arms ($p = 0.904$). Grades 3–4 treatment-related acute toxicities were increased with the addition of oxaliplatin (24% vs. 8%; $p < 0.001$) [11]. In the German CAO/ARO/AIO-04 trial, pCR was achieved in 17% of the patients who underwent surgery in the 5-FU plus oxaliplatin group and in 13% of the patients who underwent surgery in the fluorouracil group ($p = 0.038$) [78]. Unlike the previously mentioned studies, grade 3–4 toxicities were not significantly different between the arms, and pCR was higher in 5-FU plus oxaliplatin group. Longer follow-up is required to show the effect on DFS. In the PETACC-6 trial, pCR rates in both arms were 11.3% in capecitabine alone and 13.3% in the oxaliplatin group ($p = 0.31$) [57]. Grade 3/4 toxicity occurred in 15.1% of patients in capecitabine group and 36.7% in the oxaliplatin group. For clear evaluation, we should wait for the study end points to be reported in the future.

Irinotecan is an accepted chemotherapeutic agent in advanced RC that was also studied in a neoadjuvant setting. In the RTOG 0012 trial, the addition of irinotecan did not increase the pathological response rate. Acute and late toxicities were similar in each arm [79]. In the RTOG 0247 trial, the pCR rates were 10% in the irinotecan group and 18% in the oxaliplatin group. Like oxaliplatin, irinotecan was found to be ineffective with regard to neoadjuvant treatment of rectal cancer with increased toxicities [80].

The current widely used approach as evidenced by the aforementioned clinical trials is the use of neoadjuvant CRT using a fluoropyrimidine concurrent with RT. However, with the improvements in the drug regimens in treating metastatic disease, the role of systemic therapy prior to surgery is now being considered. Such therapy with combinations of fluoropyrimidine and either oxaliplatin or irinotecan will offer better systemic disease control and possibly local disease control comparable to a fluoropyrimidine-RT regimen. Schrag et al. argued that "neoadjuvant CRT delays the administration of optimal CT in stage II to III RC" [81]. In an innovative pilot study, outcomes with neoadjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin)/bevacizumab were assessed with selective use of CRT, and the investigators concluded that for selected patients with clinically staged-II to III RC, neoadjuvant CT and selective RT does not seem to compromise outcomes [81]. This strategy is now being continued into a phase III Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT, NCT01515787) trial (see Fig. 9.1) [82]. The challenge for the design of the trials of RC is the pelvic radiation, which can be associated with short- and long-term major morbidities [82]. Neoadjuvant CRT may also overtreat some patients whose risk of LR is low after TME alone [83]. For eligible patients, chemotherapy alone may also provide a significant benefit in terms of local control [84].

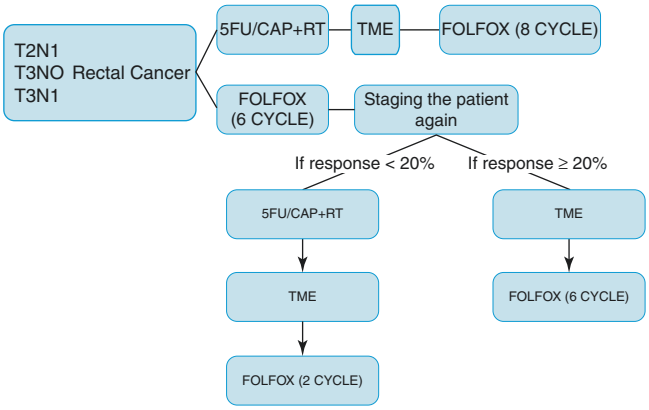


Fig. 9.1 PROSPECT is the acronym for preoperative radiation or selective preoperative radiation and evaluation before chemotherapy and Total Mesorectal Excision (TME) [81]. This trial (NCT01515787) is ongoing and should help further clarify the role of neoadjuvant systemic chemotherapy alone without radiotherapy

Targeted Agents

Epidermal growth factor receptor (EGFR) inhibitors were studied in neoadjuvant treatment of rectal adenocarcinoma because of their efficacy in metastatic CRC in tumors with wild-type RAS. Cetuximab, an anti-EGFR monoclonal antibody, demonstrated significant benefit in metastatic CRC [85, 86]. In a phase II clinical trial, 31 patients with LARC received cetuximab and capecitabine concomitantly with 45 Gy RT prior to surgery. Addition of cetuximab to capecitabine-RT, though well tolerated, did not improve the pCR rate [87].

A phase II study, S0713 investigated whether addition of cetuximab to standard Neo-CRT improves pCR in 83 LARC and Kras-wild-type patients. Cetuximab was added to induction CT of oxaliplatin and capecitabine, followed by Neo-CRT. Induction chemotherapy and Neo-CRT with cetuximab improved pCR to approximately 20% [88]. Encouraging results were also seen with gefitinib, a potent EGFR tyrosine kinase inhibitor when combined with both CT and RT in preclinical studies [89]. An Italian study of 41 patients with uT3/T4 or uN+, who received a combination of prolonged intravenous infusion of 5-FU and gefitinib with pelvic RT, reported a pCR rate of 30% [90]. However, significant grade 3 toxicity was seen; 21% were gastrointestinal, 26% hepatic, and 61% of patients required a dose reduction. In another phase I/II trial, gefitinib was administered concomitant with preoperative RT in 20 patients with LARC; 5 patients had pCR (20%) [91]. At this time, oral tyrosine kinase inhibitors targeting EGFR are being developed further in this neoadjuvant setting. The efficacy of panitumumab in patients with RAS wild-type metastatic colorectal carcinoma has been shown in several phase III studies [92, 93]. The phase II trial SAKK 41/07 investigated the addition of panitumumab (P)

to neoadjuvant capecitabine and external beam RT [76]. Pathological near-complete or complete tumor response was achieved in 21 patients (53%) treated with P + CRT versus 9 patients (32%) treated with CRT alone. This study showed that the addition of panitumumab to neoadjuvant CRT in patients with KRAS wild-type LARC resulted in higher near or complete pathological response rates, suggesting the need for a larger randomized trial.

An anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab is widely used in the treatment of metastatic CRC patients [94, 95]. Bevacizumab has been investigated in CRT studies in RC. In the AVACROSS trial, the addition of bevacizumab to XELOX (capecitabine plus oxaliplatin) induction therapy and concomitant capecitabine-RT in LARC was investigated [96]. A selected 47 patients were enrolled to this study, 34% of whom achieved a pCR. The pCR rates were lower in the GEMCAD-GCR3 study [97] in which a pCR of only 14% was found after induction therapy with XELOX, concomitant XELOX-RT followed by surgery. It is possible that the addition of bevacizumab provides higher efficacy for pCR. There are also some concerns that the combination of bevacizumab and radiation may increase surgical morbidity. A phase II study of 5-FU, aflibercept (which binds to VEGF-A, VEGF-B, and placental growth factor), and RT for the preoperative and adjuvant treatment of stage II/III RC was presented at the 2015 American Society of Clinical Oncology (ASCO) meeting. This treatment was well tolerated, but did not show a different pCR rate from historical data [98].

How to Optimize Adjuvant and Neoadjuvant Therapy?

As discussed earlier, LR risk is a concern in patients with stage II–III rectal cancer. This is partly explained by the anatomical location of the rectum being close to the pelvic organs. Downsizing of the tumor and associated lymph nodes improves the chances of negative margins, sphincter-sparing surgery in low and intermediate lying tumors, and reduces some of the acute and long-term morbidities of RT (compared to postoperative CRT) [59]. Hence, neoadjuvant treatment consisting of CT and RT is the treatment of choice in patients with LARC (T3 N0, or TanyNpositive) especially in those where preoperative staging assessments suggest the presence of mesorectal invasion [99].

In a phase III trial, investigators studied capecitabine or 5-FU by CVI concurrent with RT (50.4 Gy) in 392 patients with stage II–III RC who were given treatments in either a neoadjuvant or adjuvant setting in a randomized fashion. There was no difference in the LR rate or OS between the study arms. However, patients receiving capecitabine had increased rates of tumor downstaging (55% vs. 39%) and pathological node-negative rates (71% vs. 56%) compared to those receiving CVI 5-FU. Patients receiving capecitabine also had significantly more hand-foot skin reactions in any grade (31% vs. 2%), but lesser neutropenia (35% vs. 25%) [100]. Geva et al. found no advantage for the administration of adjuvant CT with regard to either DFS or OS. It is commonly considered that the use of postoperative RT in addition to CT increases survival in the patients with pathologically staged II or III rectal carcinoma [101]. The efficacy of postoperative RT and 5-FU-based CT for the patients was established by a series of prospective, randomized clinical trials [102–105].

MRI and EUS are tools to clinically determine the stage of rectal cancer. The question is whether we must use clinical staging before surgery for adjuvant treatment decisions. We must keep in mind the possibilities of erroneous tumor staging using either MRI or EUS that may include over- or under-staging. As an example, clinical stage I in a preoperative setting at times may be found to be pathological stage II or even III. A consensus established by the National Comprehensive Cancer Network (NCCN) panel was as follows: Preoperative CRT must be performed for patients with clinically staged-II//III RC. Postoperative CRT is recommended when stage I RC is pathologically staged-II or III after surgery [106]. In addition, following neoadjuvant CRT and surgical resection for clinically staged-II/III RC, the NCCN guidelines recommend adjuvant CT that is independent from the results of surgical pathology staging.

Patients whose primary tumors are located high in the rectum and are clinically staged T3 N0 disease are in a lower risk group [107]. After CRT, little benefit may be derived from additional postoperative chemotherapy in these low-risk patients. However, if these patients underwent radical resection without neoadjuvant chemoradiation, adjuvant chemotherapy may be considered.

Role of Surgery in Clinical Stage T0N0 After Neoadjuvant Therapy

Morbidity, mortality, and stoma construction problems may complicate the surgery for rectal cancer. Organ-preserving treatments may provide equivalent oncological outcomes with the standard treatment modalities in rectal cancer. The major advantage of no surgery after neoadjuvant therapy is to avoid a permanent colostomy, especially in low-lying rectal tumors. Some researchers investigated the benefit of surgery in patients who had clinical stage 0 after CRT. This alternative approach has been the concept of nonoperative surveillance, which was termed “watch and wait.” This strategy is based on the diagnosis of a clinical complete response (cCR) in which there is no evidence of detectable tumor at clinical and radiological re-assessment following neoadjuvant CRT [108].

Habr-Gama et al. determined that surgery was necessary in patients with clinical stage 0 RC [109]. They compared the outcomes of complete responders with or without surgery. Following CRT, 71 patients (26.8%) who had complete clinical response were observed without surgery. The 5-year overall survival rates were 88% and 83% in the resection group and in the observation group, and DFS rates were 100% and 92%, respectively. Smith et al. suggested that clinical complete response determined by radiology may provide similar prognostic value as a pathological compete response [110]. Reliable and consistent identification of stage 0 disease after CRT for distal RC is essential to define a subset of patients that may be managed by close observation alone and without surgical resection and permanent colostomy. Patients with cT2N0 rectal cancer are more likely to develop complete response to neoadjuvant CRT [111]. Radiation dose-escalation and consolidation chemotherapy have been associated with increased rates of response and may improve chances of organ preservation among these patients. cT2N0 patients undergoing extended CRT were more likely to undergo organ preservation and avoid definitive surgical resection at 5 years (67% vs. 30%; $p = 0.001$) [111]. The Memorial Sloan Kettering Cancer Centre (MSKCC) is currently running a phase II study in which patients are randomized between induction chemotherapy followed by nCRT, and nCRT followed by consolidation chemotherapy (https://clinicaltrials.gov/ct2/show/NCT02008656). Patients with a significant clinical response to treatment are being managed with a non-operative strategy. The PROSPECT trial [82] (NCT01515787) is ongoing and should help further clarify the role of neoadjuvant systemic chemotherapy alone. If organ preservation is sought, radiotherapy should currently be included in the treatment strategy.

In the absence of stronger evidence toward a precise time point, clinicians who are considering watch and wait for their patients should organize response assessment investigation between 6 and 12 weeks after the completion of treatment. Patients who have shown some degree of response might actually benefit from longer waiting and perhaps consolidation chemotherapy in some of them [112]. The new European Society for Medical Oncology (ESMO) guidelines do not routinely recommend adjuvant treatment in RC [113]. Positron emission tomography (PET) and computed tomography scans were found to be inadequate in distinguishing complete from partial responders [114]. Magnetic resonance imaging can be used to predict tumor regression grade after CRT [115]. Of note, residual tumors were located at the invasive front or submucosal layer of the rectum, suggesting that endoscopic biopsies are not useful. A full-thickness or excisional biopsy could detect residual malignancy more accurately [116]. Neither endoscopic nor full-thickness biopsies guarantee the confirmation of a complete response in lymph nodes. The surveillance protocol includes a combination of clinical examination, monitoring of CEA level, flexi-sigmoidoscopy, and/or complete colonoscopy and imaging exams. No clear recommendation as to the best surveillance program has been defined, but several series have reported that the vast majority of regrowths occur in the first 2 years after completion of treatment. Most groups of investigators have opted for clinical visits and exams every 1–3 months for the first 2 years.

Dossa and colleagues did a systematic review and meta-analysis on the safety and outcomes of a watch and wait approach in patients achieving cCR [117]. They defined local regrowth as evidence of intraluminal tumor detected clinically, endoscopically, or radiologically. Nodal disease was considered as non-regrowth recurrence, which also included any non-luminal intrapelvic disease or distant metastatic disease. The pooled rate of local regrowth was 15.7% (95% CI 11.8–20.1), and following a regrowth, the pooled rate of salvage therapy was 95.4% (95% CI 89.6–99.3). For those patients undergoing salvage surgery, the rate of sphincter preservation was 49.8% (95% CI 33.0–66.6). Compared to patients managed with surgery, patients being followed in a watch and wait protocol did not have any significant difference in non-regrowth recurrence, cancer-specific mortality and overall survival.

Kong et al. found the rate of tumor regrowth was 28.4%, with a rate of salvage surgery of 83.8%. The rate of distant recurrence without tumor regrowth was 1.9% [118]. The rate of distant recurrence was similar between patients in the watch and wait group and patients having immediate surgery. Disease-free survival and overall survival differed between studies, but it ranged from 97% at 2 years to 91% at 5 years for OS, and 88% at 2 years to 68% at 5 years for DFS, without any significant difference when compared to patients having a pCR after immediate surgery. The International Watch and Wait Data Base reported, with a median follow-up time of 2.6 years, that the rate of local regrowth was 25%, and 84% of these regrowths occurred in the first 2 years after treatment [119]. Ninety-six percent (96%) of the regrowths were intraluminal, and 4% were locoregional nodal recurrence. Seven percent (7%) of patients developed distant metastatic disease. The OS at 3 years was 91%. Despite these impressive results, the NCCN panel does not support this approach in the routine management of localized rectal cancer. Moreover, one of the main concerns with watch and wait is the lack of long-term data, especially on patients who experience regrowth, to confirm the safety of this approach. A randomized controlled study, such as the TRIGGER trial, should provide more reliable answers [120].

At this time, an organ-sparing strategy of a watch and wait approach needs further consideration. This approach must be used in very selected patients with distal tumors in whom poor functional anal sphincter outcome is to be expected and

who are expected to be compliant with stringent follow-up. In addition, patients who have major morbidities and poor performance status may also be candidates.

Total Neoadjuvant Therapy

In many trials, compliance with adjuvant therapy after surgery was poor [121]. The most common reason for the poor adjuvant chemotherapy compliance was treatment-related/postoperative toxicities. On the other hand, neoadjuvant chemotherapy (NAC) may allow for greater treatment compliance with reducing toxicity rates. Earlier delivery of full-dose, systemic therapy to eliminate micrometastatic disease has the potential to improve disease-related outcomes [122].

Total neoadjuvant therapy (TNT) with neoadjuvant chemotherapy can also facilitate the selection of patients who may benefit from organ preservation or a watch and wait approach. Two neoadjuvant paradigms have emerged from the literature: () CRT followed by NAC, and (2) NAC followed by CRT. Multiple prospective studies have reported that neoadjuvant chemotherapy improved compliance rates, reduced toxicity, and decreased distant relapse rate. Adding chemotherapy after chemoradiotherapy can increase the complete clinical response rate [122]. One study showed substantial improvement in the complete clinical response rate with chemotherapy after CRT, in which the pathological complete response rate was doubled [123].

A TNT approach could increase the proportion of patients with rectum cancer who are eligible for organ preservation. Validation and optimization of a TNT approach with future studies is needed.

Conclusion

A multidisciplinary team approach is essential in the management of localized RC. Investigators have extensively studied the role of trimodality therapy and optimal sequencing of various treatments in the management of patients with RC. At this time, preoperative CRT has become the standard of care for the patients with node-positive disease or clinically staged T3 or T4. Preoperative CRT is associated with enhanced sphincter preservation, significant tumor, and nodal downstaging, improved acute and late tolerability, and improved local control but similar survival. 5-FU and its pro-drug capecitabine in combination with RT continue to be the reference standard for LARC treated preoperatively. Development of efficacious combination therapy regimens for advanced CRC has encouraged the incorporation of these regimens in the neoadjuvant setting. Organ preservation has been an increasing area of research interest. A subset of patients who achieve a T0N0 disease following neoadjuvant therapy may be spared radical surgical resection.

References

1. Bailey CE, Hu C-Y, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010. JAMA Surg. 2015;150:17.
2. Musio D, De Felice F, Bulzonetti N, Guarnaccia R, Caiazzo R, Bangrazi C, et al. Neoadjuvant-intensified treatment for rectal cancer: time to change? World J Gastroenterol. 2013;19:3052–61.
3. Bosset J-F. Adjuvant treatment of rectal cancer: improving patient selection. Gastrointest Cancer Res. 2008;2:37–8.
4. Kornmann M, Staib L, Wiegel T, Kreuser E-D, Kron M, Baumann W, et al. Adjuvant chemoradiotherapy of advanced resectable rectal cancer: results of a randomised trial comparing modulation of 5-fluorouracil with folinic acid or with interferon-α. Br J Cancer. 2010;103:1163–72.
5. Samee A, Selvasekar CR. Current trends in staging rectal cancer. World J Gastroenterol. 2011;17:828–34.
6. De Divitiis C, Nasti G, Montano M, Fisichella R, Iaffaioli RV, Berretta M. Prognostic and predictive response factors in colorectal cancer patients: between hope and reality. World J Gastroenterol. 2014;20:15049–59.
7. Hansen MH, Balteskard L, Dørum LM, Eriksen MT, Vonen B. Locally recurrent rectal cancer in Norway. Br J Surg. 2009;96:1176–82.
8. Lemmens V, van SL, Janssen-Heijnen M, Martijn H, Rutten H, Coebergh JW. Trends in colorectal cancer in the south of the Netherlands 1975–2007: rectal cancer survival levels with colon cancer survival. Acta Oncol (Madr). 2010;49:784–96.
9. Bosset J-F, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355:1114–23.
10. Gerard J-P. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006;24:4620–5.
11. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol. 2011;29:2773–80.
12. Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant Oxaliplatin, Capecitabine, and preoperative radiotherapy with or without Cetuximab followed by total Mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol. 2012;30(14):1620–7.
13. Gérard J-P, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne P-L, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol. 2010;28:1638–44.
14. Leighl N, Gattellari M, Butow P, Brown R, Tattersall MH. Discussing adjuvant cancer therapy. J Clin Oncol. 2001;19:1768–78.
15. Benson AB, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22:3408–19.
16. Sterzing F, Hoehle F, Ulrich A, Jensen A, Debus J, Muenter M. Clinical results and toxicity for short-course preoperative radio-

therapy and total mesorectal excision in rectal cancer patients. J Radiat Res. 2014;56:169–76.
17. Bipat S, Glas AS, Slors FJM, Zwinderman AH, Bossuyt PMM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging–a meta-analysis. Radiology. 2004;232:773–83.
18. Suzuki C, Torkzad MR, Tanaka S, Palmer G, Lindholm J, Holm T, et al. The importance of rectal cancer MRI protocols on iInterpretation accuracy. World J Surg Oncol. 2008;6:89.
19. MERCURY Study Group. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. Radiology. 2007;243:132–9.
20. Persiani R, Biondi A, Pennestrì F, Fico V, De Simone V, Tirelli F, et al. Transanal total mesorectal excision vs laparoscopic total mesorectal excision in the treatment of low and middle rectal cancer: a propensity score matching analysis. Dis Colon Rectum. 2018;61(7):809–16.
21. Heald RJ. A new approach to rectal cancer. Br J Hosp Med. 1979;22:277–81.
22. Cass AW, Million RR, Pfaff WW. Patterns of recurrence following surgery alone for adenocarcinoma of the colon and rectum. Cancer. 1976;37:2861–5.
23. Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum. Clinicopathologic correlation and implications for adjuvant therapy. Cancer. 1974;34:1278–92.
24. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
25. Lin H-H, Lin J-K, Lin C-C, Lan Y-T, Wang H-S, Yang S-H, et al. Circumferential margin plays an independent impact on the outcome of rectal cancer patients receiving curative total mesorectal excision. Am J Surg. 2013;206:771–7.
26. Tocchi A, Mazzoni G, Lepre L, Liotta G, Costa G, Agostini N, et al. Total mesorectal excision and low rectal anastomosis for the treatment of rectal cancer and prevention of pelvic recurrences. Arch Surg. 2001;136:216–20.
27. Wibe A, Eriksen MT, Syse A, Myrvold HE, Søreide O. Total mesorectal excision for rectal cancer–what can be achieved by a national audit? Color Dis. 2003;5:471–7.
28. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet. 2005;365(9472):1718–26.
29. van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, et al. COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol. 2013;14(3):210–8.
30. Jeong SY, Park JW, Nam BH, Kim S, Kang SB, Lim SB, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol. 2014;15(7):767–74.
31. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, et al. COLOR II Study Group. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med. 2015;372(14):1324–32.
32. Stevenson AR, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, et al. ALaCaRT investigators. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. JAMA. 2015;314(13):1356–63.
33. Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. JAMA. 2015;314(13):1346–55.
34. Jayne D, Pigazzi A, Marshall H, Croft J, Corrigan N, Copeland J, et al. Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: the ROLARR randomized clinical trial. JAMA. 2017;318(16):1569–80.
35. de Lacy AM, Rattner DW, Adelsdorfer C, Tasende MM, Fernández M, Delgado S, et al. Transanal natural orifice transluminal endoscopic surgery (NOTES) rectal resection: "down-to-up" total mesorectal excision (TME)–short-term outcomes in the first 20 cases. Surg Endosc. 2013;27(9):3165–72.
36. Deijen CL, Velthuis S, Tsai A, Mavroveli S, de Lange-de Klerk ES, Sietses C, et al. COLOR III: a multicentre randomised clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer. Surg Endosc. 2016;30(8):3210–5.
37. no authors listed. Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Rectal Cancer Study Group. Cancer. 1990;66(1):49–55.
38. Gérard A, Buyse M, Nordlinger B, Loygue J, Pène F, Kempf P, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg. 1988;208:606–14.
39. Goldberg PA, Nicholls RJ, Porter NH, Love S, Grimsey JE. Long-term results of a randomised trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure. Eur J Cancer. 1994;30A:1602–6.
40. Jones DJ, Zaloudik J, James RD, Haboubi N, Moore M, Schofield PF. Predicting local recurrence of carcinoma of the rectum after preoperative radiotherapy and surgery. Br J Surg. 1989;76:1172–5.
41. Horn A, Halvorsen JF, Dahl O. Preoperative radiotherapy in operable rectal cancer. Dis Colon Rectum. 1990;33:823–8.
42. Rider WD, Palmer JA, Mahoney LJ, Robertson CT. Preoperative irradiation in operable cancer of the rectum: report of the Toronto trial. Can J Surg. 1977;20:335–8.
43. Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst. 1988;80:21–9.
44. Balslev I, Pedersen M, Teglbjaerg PS, Hanberg-Soerensen F, Bone J, Jacobsen NO, et al. Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid. A randomized multicenter study. Cancer. 1986;58:22–8.
45. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med. 1985;312:1465–72.
46. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. 1991;324:709–15.
47. Glimelius B, Isacsson U, Jung B, Påhlman L. Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose-response effect favoring preoperative treatment. Int J Radiat Oncol Biol Phys. 1997;37:281–7.
48. Påhlman L, Glimelius B. The value of adjuvant radio(chemo)therapy for rectal cancer. Eur J Cancer. 1995;31A:1347–50.
49. Siegel R, Burock S, Wernecke K-D, Kretzschmar A, Dietel M, Loy V, et al. Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cancer: a multi-centre prospectively randomised study of the Berlin Cancer Society. BMC Cancer. 2009;9:50.
50. Cedermark B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. Cancer. 1995;75:2269–75.

51. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer. 2001;92:896–902.
52. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345:638–46.
53. Kusters M, Marijnen CAM, van de Velde CJH, Rutten HJT, Lahaye MJ, Kim JH, et al. Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial. Eur J Surg Oncol. 2010;36:470–6.
54. Roels S, Duthoy W, Haustermans K, Penninckx F, Vandecaveye V, Boterberg T, et al. Definition and delineation of the clinical target volume for rectal cancer. Int J Radiat Oncol Biol Phys. 2006;65:1129–42.
55. Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, Glimelius B, Påhlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336:980–7.
56. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet (London, England). 1993;341:457–60.
57. ASCO Annual Meeting 2013. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: first results of the PETACC-6 randomized phase III trial. In: 2013 ASCO Annual Meeting. Abstracts. 2013.
58. [no authors listed]. Radiation therapy and fluorouracil with or without semustine for the treatment of patients with surgical adjuvant adenocarcinoma of the rectum. Gastrointestinal Tumor Study Group. J Clin Oncol. 1992;10:549–57.
59. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30:1926–33.
60. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40.
61. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27:5124–30.
62. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93:1215–23.
63. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group Trial 01.04. J Clin Oncol. 2012;30:3827–33.
64. Thomas PR, Lindblad AS. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience. Radiother Oncol. 1988;13:245–52.
65. Wolmark N, Wieand HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: national surgical adjuvant breast and bowel project protocol R-02. J Natl Cancer Inst. 2000;92:388–96.
66. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009;373:811–20.
67. ASCO Annual Meeting 2015. A phase II single arm feasibility trial of neoadjuvant chemotherapy (NAC) with oxaliplatin/fluorouracil (OxMdG) then short-course preoperative radiotherapy (SCPRT) then immediate surgery in operable rectal cancer (ORC): COPERNICUS (NCT01263171). AS 2015.
68. Deng Y, Chi P, Lan P, Wang L, Cui L, Chen D, et al. A multicenter randomized controlled trial of mFOLFOX6 with or without radiation in neoadjuvant treatment of local advanced rectal cancer (FOWARC study): preliminary results. In: 2015 ASCO Annual Meeting, Abstracts, Meeting Library. 2015.
69. Frykholm GJ, Påhlman L, Glimelius B. Combined chemo- and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiat Oncol Biol Phys. 2001;50:427–34.
70. Pettersson D, Cedermark B, Holm T, Radu C, Påhlman L, Glimelius B, et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg. 2010;97:580–7.
71. Allegra CJ, Yothers G, O'Connell MJ, Roh MS, Beart RW, Petrelli NJ, et al. Neoadjuvant therapy for rectal cancer: mature results from NSABP protocol R-04. 2014 Gastrointestinal Cancers Symposium, Abstracts, Meeting Library 2014. J Clin Oncol. 2014;32 (suppl 3; abstr 390).
72. Roh MS, Yothers GA, O'Connell MJ, Beart RW, Pitot HC, Shields AF, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. ASCO Meet Abstr. 2011;29(15_suppl):3503.
73. Rödel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, et al. German Rectal Cancer Study Group. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2015;16(8):979–89.
74. Jung M, Shin SJ, Koom WS, Jung I, Keum KC, Hur H, et al. A randomized phase 2 study of neoadjuvant chemoradiaton therapy with 5-Fluorouracil/Leucovorin or Irinotecan/S-1 in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2015;93(5):1015–22.
75. Landry JC, Feng Y, Prabhu RS, Cohen SJ, Staley CA, Whittington R, et al. Phase II trial of preoperative radiation with concurrent Capecitabine, Oxaliplatin, and Bevacizumab followed by surgery and postoperative 5-Fluorouracil, Leucovorin, Oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: 5-year clinical outcomes ECOG-ACRIN Cancer Research Group E3204. Oncologist. 2015;20(6):615–6.
76. Helbling D, Bodoky G, Gautschi O, Sun H, Bosman F, Gloor B, et al. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. Ann Oncol. 2013;24(3):718–25.
77. Mohiuddin M, Regine WF, John WJ, Hagihara PF, McGrath PC, Kenady DE, et al. Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. Int J Radiat Oncol Biol Phys. 2000;46:883–8.
78. Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol. 2012;13:679–87.
79. Mohiuddin M, Winter K, Mitchell E, Hanna N, Yuen A, Nichols C, et al. Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group Trial 0012. J Clin Oncol. 2006;24:650–5.
80. Wong SJ, Winter K, Meropol NJ, Anne PR, Kachnic L, Rashid A, et al. Radiation Therapy Oncology Group 0247: a randomized phase II study of neoadjuvant capecitabine and irinotecan or capecitabine

and oxaliplatin with concurrent radiotherapy for patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2012;82:1367–75.
81. Schrag D, Weiser MR, Goodman KA, Gonen M, Hollywood E, Cercek A, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol. 2014;32:513–8.
82. NCT01515787 CT. PROSPECT: chemotherapy alone or chemotherapy plus radiation therapy in treating patients with locally advanced rectal cancer undergoing surgery. https://clinicaltrials.gov/ct2/show/NCT01515787 Accessed 13 June 2018.
83. Hong TS, Kachnic LA. Preoperative chemoradiotherapy in the management of localized rectal cancer: the new standard. Gastrointest Cancer Res. 2007;1:49–56.
84. Trakarnsanga A. Treatment of locally advanced rectal cancer: controversies and questions. World J Gastroenterol. 2012;18:5521.
85. Van Cutsem E, Köhne C-H, Hitre E, Zaluski J, Chang Chien C-R, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360:1408–17.
86. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009;27:663–71.
87. Eisterer W, De Vries A, Öfner D, Rabl H, Koplmüller R, Greil R, et al. Preoperative treatment with capecitabine, cetuximab and radiotherapy for primary locally advanced rectal cancer–a phase II clinical trial. Anticancer Res. 2014;34:6767–73.
88. Leichman CG, McDonough SL, Smalley SR, Billingsley KG, Lenz H-J, Beldner MA, et al. S0713: a phase II study of cetuximab (CET) added to induction chemotherapy (ICT) of oxaliplatin (OX) and capecitabine (CAP), followed by neoadjuvant chemoradiation (NACR) for locally advanced rectal cancer (LARC). 2015 ASCO Annual Meeting, Abstracts. J Clin Oncol. 2015;33 (Suppl; Abstr 3516).
89. Williams KJ, Telfer BA, Stratford IJ, Wedge SR. ZD1839 ("Iressa"), a specific oral epidermal growth factor receptor-tyrosine kinase inhibitor, potentiates radiotherapy in a human colorectal cancer xenograft model. Br J Cancer. 2002;86:1157–61.
90. Valentini V, De Paoli A, Gambacorta MA, Mantini G, Ratto C, Vecchio FM, et al. Infusional 5-fluorouracil and ZD1839 (Gefitinib-Iressa) in combination with preoperative radiotherapy in patients with locally advanced rectal cancer: a phase I and II trial (1839IL/0092). Int J Radiat Oncol Biol Phys. 2008;72:644–9.
91. Allal AS, Roth AD, Franzetti-Pellanda A, Bonet M, Gervaz P, Bieri S. Phase I/II study of Gefitinib and concomitant preoperative radiotherapy in patients with locally advanced rectal cancer. J Cancer Ther. 2012;3:970–6.
92. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25:1658–64.
93. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26:1626–34.
94. Kabbinavar FF, Hurwitz HI, Yi J, Sarkar S, Rosen O. Addition of bevacizumab to fluorouracil-based first-line treatment of metastatic colorectal cancer: pooled analysis of cohorts of older patients from two randomized clinical trials. J Clin Oncol. 2009;27:199–205.
95. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.
96. Nogué M, Salud A, Vicente P, Arriví A, Roca JM, Losa F, et al. Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging-defined poor-prognosis locally advanced rectal cancer: the AVACROSS study. Oncologist. 2011;16:614–20.
97. Fernández-Martos C, Pericay C, Aparicio J, Salud A, Safont M, Massuti B, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, l. J Clin Oncol. 2010;28:859–65.
98. Acs P, Thompson DS, Hemphill M., Wenk D, Bendell J., Kennedy A. A phase II study of 5-fluorouracil (5-FU), ziv-aflibercept, and radiation for the preoperative and adjuvant treatment of patients (pts) with stage II/III rectal cancer. 2015 ASCO Annual Meeting, Abstracts, Meeting Library. J Clin Oncol. 2015;33 (Suppl; Abstr 3607).
99. Chau I. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol. 2006;24:668–74.
100. Hofheinz R-D, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012;13:579–88.
101. Geva R, Itzkovich E, Shamai S, Shacham-Shmueli E, Soyfer V, Klausner JM, et al. Is there a role for adjuvant chemotherapy in pathological complete response rectal cancer tumors following neoadjuvant chemoradiotherapy? J Cancer Res Clin Oncol. 2014;140:1489–94.
102. O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med. 1994;331:502–7.
103. Smalley SR. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol. 2006;24:3542–7.
104. Tepper JE, O'Connell M, Niedzwiecki D, Hollis DR, Benson AB, Cummings B, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control–final report of intergroup 0114. J Clin Oncol. 2002;20:1744–50.
105. Gunderson LL, Sargent DJ, Tepper JE, Wolmark N, O'Connell MJ, Begovic M, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol. 2004;22:1785–96.
106. Benson AB, Venook AP, Bekaii-Saab T, Chan E, Chen Y-J, Cooper HS, et al. Rectal cancer, version 2.2015. J Natl Compr Cancer Netw. 2015;13:719–28; quiz 728.
107. Gunderson LL, Sargent DJ, Tepper JE, O'Connell MJ, Allmer C, Smalley SR, et al. Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer: a pooled analysis. Int J Radiat Oncol Biol Phys. 2002;54(2):386–96.
108. Dattani M, Heald RJ, Goussous G, Broadhurst J, São Julião GP, Habr-Gama A, et al. Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and pooled analysis. Ann Surg. 2018;268:955–67. (Epub ahead of print).
109. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Silva e Sousa AH, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240:711–-8.
110. Smith J, Chow O, Eaton A, Widman M, Nash G, Temple LKF, et al. Organ preservation in patients with rectal cancer with clinical complete response after neoadjuvant therapy. | 2015

Gastrointestinal Cancers Symposium, Abstracts, Meeting Library. J Clin Oncol. 2015;33 (Suppl 3; Abstr 509).
111. Habr-Gama A, São Julião GP, Vailati BB, Sabbaga J, Aguilar PB, Fernandez LM, et al. Organ preservation in cT2N0 rectal cancer after neoadjuvant chemoradiation therapy: the impact of radiation therapy dose-escalation and consolidation chemotherapy. Ann Surg. 2017;24:102–7. (Epub ahead of print).
112. Bernier L, Balyasnikova S, Tait D, Brown G. Watch-and-wait as a therapeutic strategy in rectal cancer. Curr Colorectal Cancer Rep. 2018;14(2):37–55.
113. Glimelius B, Tiret E, Cervantes A, Arnold D. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24:vi81–8.
114. Guillem JG, Ruby JA, Leibold T, Akhurst TJ, Yeung HW, Gollub MJ, et al. Neither FDG-PET Nor CT can distinguish between a pathological complete response and an incomplete response after neoadjuvant chemoradiation in locally advanced rectal cancer: a prospective study. Ann Surg. 2013;258(2):289–95.
115. Patel UB, Taylor F, Blomqvist L, George C, Evans H, Tekkis P, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol. 2011;29(28):3753–60.
116. Duldulao MP, Lee W, Streja L, Chu P, Li W, Chen Z, et al. Distribution of residual cancer cells in the bowel wall after neoadjuvant chemoradiation in patients with rectal cancer. Dis Colon Rectum. 2013;56(2):142–9.
117. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017;2(7):501–13.
118. Kong JC, Guerra GR, Warrier SK, Ramsay RG, Heriot AG. Outcome and salvage surgery following “watch and wait” for rectal cancer after neoadjuvant therapy: a systematic review. Dis Colon Rectum. 2017;60(3):335–45.
119. van der Valk M. The International Watch & Wait database (IWWD) for rectal cancer: an update. J Clin Oncol. 2017;35(4_suppl):521.
120. Battersby NJ, Dattani M, Rao S, Cunningham D, Tait D, Adams R, et al. A rectal cancer feasibility study with an embedded phase III trial design assessing magnetic resonance tumour regression grade (mrTRG) as a novel biomarker to stratify management by good and poor response to chemoradiotherapy (TRIGGER): study protocol for a randomised controlled trial. Trials. 2017;18(1):394.
121. Sainato A, Cernusco Luna Nunzia V, Valentini V, De Paoli A, Maurizi ER, Lupattelli M, et al. No benefit of adjuvant fluorouracil leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). Radiother Oncol. 2014;113(2):223–9.
122. Ludmir EB, Palta M, Willett CG, Czito BG. Total neoadjuvant therapy for rectal cancer: an emerging option. Cancer. 2017;123(9):1497–506.
123. Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Timing of rectal cancer response to chemoradiation consortium. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015;16(8):957–66.

Squamous Cell Carcinoma of the Anal Canal

10

Shahab Ahmed, Cathy Eng, and Craig A. Messick

Epidemiology

Squamous cell carcinoma of the anal canal (SCCA) is the major variant of anal cancer, which is considerably rare compared to the other gastrointestinal (GI) cancers. It represents only 0.4% of all new cancer diagnoses in the United States. According to the Surveillance, Epidemiology, and End Results Program (SEER), there were an estimated total of 7270 new cases and 1010 deaths due to SCCA in the United States in 2015 [1]. The median age at diagnosis and death from SCCA is 61 years and 64 years, respectively. The data also show that the overall incidence and mortality rates due to SCCA have been increasing for almost four decades (1975–2012), due to its association with the human papilloma virus (HPV) [1].

Risk Factors

In general, SCCA is more common in older people (age 55–64) and in women (2.0 per 100,000) more than in men (1.5 per 100,000), except for African-American men who have higher incidence (2.1 per 100,000) than African-American women (1.6 per 100,000) [1]. Risk factors are discussed herein.

Human Papilloma Virus

Human papilloma virus (HPV) is responsible for almost 95% of anal cancers. Among different types (more than 150), HPV-16 and HPV-18 are the two highest-risk strains for developing SCCA. Though HPV infection is mostly a sexually transmitted disease (STD) (anal, vaginal, or oral sex), other means of direct mucosal contact facilitate virus transmission, including from mother to newborn during childbirth [2], suggesting additional modes of transmission is probable.

Human Immunodeficiency Virus

Anal cancer is a non-acquired immunodeficiency syndrome (AIDS)-defining cancer (NADC) and the role of immunosuppression by human immunodeficiency virus (HIV) on developing NADC is yet debatable. But, the study has found that the incidence of SCCA is higher (40-fold to 80-fold) in the HIV-positive population [3]. Though HIV is not a direct cause of SCCA, it is evident that co-infection of HPV and other STDs are much higher in HIV-positive patients. HPV-related precancerous high-grade anal intraepithelial neoplasia (HGAIN), formerly termed anal intraepithelial neoplasia (AIN) 2 or 3, also occur with greater frequency in HIV-positive individuals [4].

Sexual Orientation

Sexual orientation and increased sexual activity impacts the development of SCCA. Two factors that carry greater risk are multiple sexual partners and anal receptive intercourse for both in men and in women – though men having sex with men have higher risk [5–7].

Smoking

Data show that smokers may be at greater risk to develop SCCA than nonsmokers [8, 9]. There is a linear correlation associated with the number of years of tobacco exposure.

S. Ahmed · C. Eng (✉)
Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: ceng@mdanderson.org

C. A. Messick
Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_10

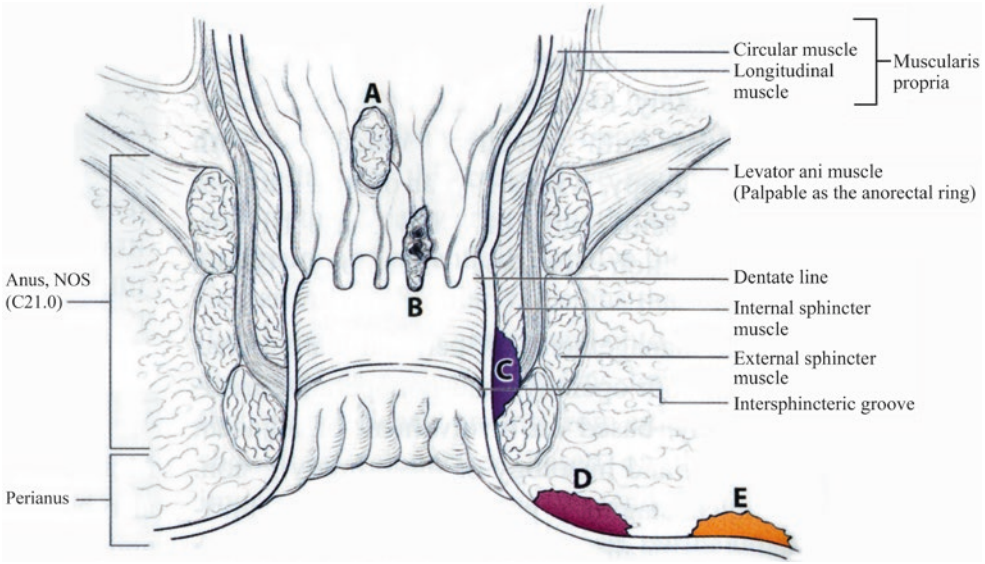


Fig. 10.1 Anal cancer (A–C), perianal cancer (D), and skin cancer (E) as visualized with gentle traction placed on the buttocks. (Used with permission of the American College of Surgeons, Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing)

History of Pelvic Radiation

Individuals who receive pelvic radiation therapy for different cancers (rectum, prostate, bladder, or cervical) are at higher risk for developing SCCA [10].

Cancer Types

Anatomically, the surgical anal canal is divided into three zones (Fig. 10.1):

- Upper colorectal zone consists of glandular epithelium
- Middle transitional zone
- Lower squamous zone

Based on the cell type, anal cancer can be divided into the following types:

Epidermoid (80%)

- Squamous cell carcinoma of the anus (SCCA) (Fig. 10.2): develops mostly in the lower anal zone, though may also occur in the anal transitional zone.

Non-epidermoid (20%)

- Adenocarcinomas: mostly occur in the upper anal zone.
- Undifferentiated.
- Basal cell carcinomas mostly occur in the anal margin.
- Melanomas, like basal cell carcinoma, develop chiefly in the anal margin.
- Gastrointestinal stromal tumors (GISTs) are very rare in the anal canal.

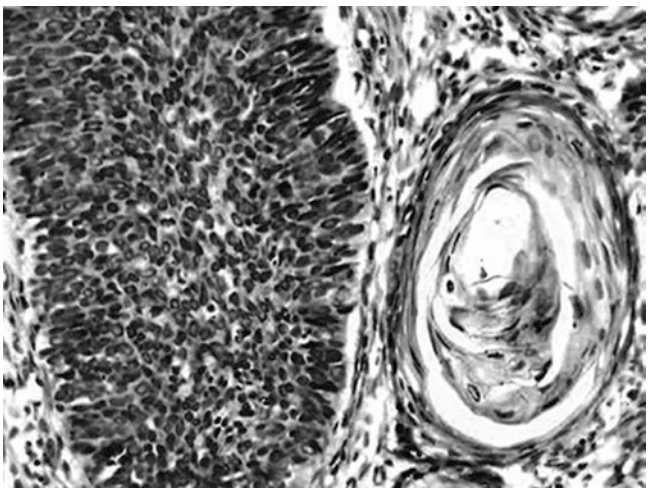


Fig. 10.2 Histopathology of squamous cell carcinoma of the anal canal. Figure shows a combination of basaloid feature and keratinization

Pathophysiology

Premalignant Squamous Cell Neoplastic Lesions

Though anatomically and functionally different, squamous cell carcinoma of the anus, cervix, vagina, and vulva all demonstrate identical development and pathologic characteristics since HPV infection is the common etiology. Moreover, the nomenclature for SCCA precursor lesions resembles that of cervical, vaginal, and vulvar dysplasia. Due to confusion among physicians, the multiple names of intraepithelial lesions

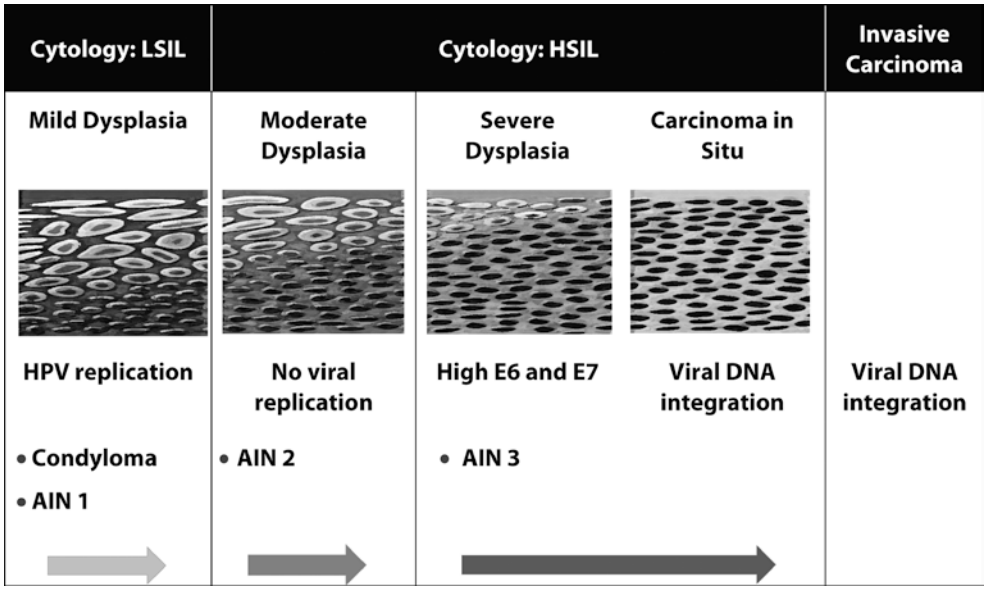


Fig. 10.3 Anal dysplasia and invasive carcinoma

have been simplified. High-grade dysplasia, Bowen's disease, AIN 2 and 3, and carcinoma in situ all represent the same histopathological findings. Thus, to avoid further confusion, they have been collectively called high-grade squamous cell intraepithelial lesions (HSIL) if they are from cytology specimens and HGAIN if they are from pathology specimens. Low-grade dysplasia and AIN 1 have been termed low-grade squamous cell intraepithelial lesions (LSIL) (cytology) and low-grade anal intraepithelial neoplasia (LGAIN) (pathology specimens) [11].

Anal dysplasia, if not treated, may progress to SCCA. Based on the severity of dysplasia, intraepithelial lesions are divided into LGAIN/LSIL, or HGAIN/HSIL. Histologically, LSILs and HSILs are characterized by low nuclear/cytoplasmic ratios (koilocytes) and high nuclear/cytoplasmic ratios, respectively. The classification of anal dysplasia based on LSILs and HSILs is outlined in Fig. 10.3.

Previous data suggested that untreated HSIL might progress to SCCA in 11% of cases and in immunocompromised patients up to 50% [12] and LSIL may progress to HSIL in the presence of risk factors such as HIV and/or anal HPV infection [4, 13, 14]. However, the current practice suggests that low grade does not progress to high grade, but what likely happens is high grade may subsequently develop in an area separate from where the low grade was at one point. The overall management of AINs is discussed under the treatment section of the chapter.

Screening

As SCCA is very rare, screening is not recommended for the general population. There are two groups of patients who are at high risk for developing HSIL and subsequent SCCA: HIV+/AIDS men who have sex with men (MSM) and transplant recipients (kidney, liver, heart, lung, and pancreas, etc.) maintained on chronic immunosuppression (prednisone, cyclosporine, tacrolimus, mycophenolate mofetil, and others). Though SCCA develops more frequently in patients not defined by these groups, identifying those "at-risk" individuals has been unsuccessful to date and therefore screening is not advocated for the general population. But, screening for high-risk individuals such as men with a history of sex with men, women with a history of cervical or vulvar cancer, HIV-positive patients, and any individual with a history of organ transplant(s) has been proven beneficial.

HPV Screening

Anal cytology obtained from anal Papanicolaou smear (Pap smear) is an important tool to demonstrate abnormalities related to HPV infection. Abnormal cytology has been reported in 9% of HSILs (Fig. 10.4) and 35% of LSILs [15]. The sensitivity of an anal cytology was 84% while its specificity was only 39% in patients with AIN 2 (a subset of HSIL). It was also mentioned that HIV+ MSM required high-resolution anoscopy (HRA) for the detection of HSILs. Currently, HIV+ MSM are recommended to undergo HRA as often as every 3 months and anal cytology annually. Outside of this group, anal cytology has not been shown to be an effective screening tool and is suggested to be used at the discretion of the treating physician.

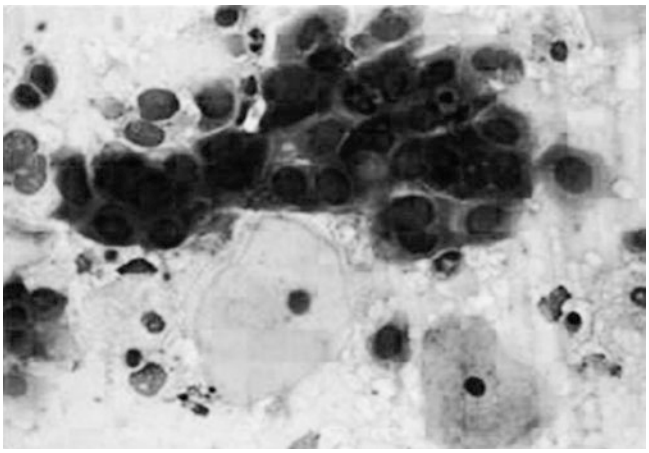


Fig. 10.4 High-grade squamous cell intraepithelial lesion (HSIL)

Diagnosis

The principle steps in diagnosing anal cancer are described as follows:

- Presence of gastrointestinal sign/symptom(s):
  - Anorectal bleeding
  - Anal pain or tenderness
  - Anal pressure
  - Anal discharge
  - Lump or growth in the anal or inguinal region
  - Change in bowel habits
  - Change in stool caliber
- Presence of associated sign/symptom(s):
  - Anemia
  - Weight loss
  - Immunosuppression or HIV+-related symptoms
  - HPV-related precancerous growths
- Physical Exam:
  - Digital rectal exam (DRE)
  - Palpate presence or absence of lymph nodes in the anal and or inguinal area
- Visualization:
  - Anoscopy
  - Rigid proctoscopy or flexible proctosigmoidoscopy
  - Endo-anal or endo-rectal ultrasound/endoscopic ultrasound (EUS)
  - Computed tomography (CT) scan
  - Positron emission tomography (PET)/CT scan
  - Magnetic resonance imaging (MRI)
- Biopsy:
  - Should be obtained during direct visualization

Staging

According to the eighth edition of the AJCC (American Joint Committee on Cancer) Cancer Staging Manual, the tumor-node-metastasis (TNM) staging system for anal cancer is described in Table 10.1 [16].

The clinical and pathologic staging is described in Table 10.2 [1].

Table 10.1 American joint committee on cancer (AJCC) tumor-node-metastasis (TNM) staging definitions for anal cancer

Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor not assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II-III, high-grade anal intraepithelial neoplasia)
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm but ≤5 cm
T3	Tumor > 5 cm
T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder

Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Used with permission of the American joint committee on cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC cancer staging manual, Eighth Edition (2017) published by Springer International Publishing

Table 10.2 Group (clinical and pathologic staging) of anal cancer

Group	TNM	5-Year relative survival
0	TisN0M0	58.6–80.1% for nonmetastatic disease [1]
I	T1N0M0	
II	T2N0M0 T3N0M0	
IIIA	T1N1M0 T2N1M0 T3N1M0 T4N0M0	
IIIB	T4N1M0 Any T and N2 M0 Any T and N3 M0	
IV	Any T, any N, M1	30.7% [1]

Treatment

The treatments of anal cancer described in this section are principally available options to manage SCCA. The management of adenocarcinoma of the anal canal resembles that of rectal cancer, which is not the focus of this chapter.

Regional

- Stage 0: These very early stage diseases can be treated completely with surgical intervention.
- Stage I and II: Small lesions less than 1 centimeter and not involving the anal sphincter can be managed operatively with negative margins. Tumors greater than 1 cm or involving the anal sphincter are managed nonsurgically with combined modality chemoradiation therapy (CMT), detailed in the next section.

Locally Advanced

Before the mid-1980s, an abdominoperineal resection (APR) was the standard of care for the management of locally advanced SCCA. The procedure obligates a permanent colostomy due to the sphincter mechanism being removed. One major problem of anal surgery is the delayed and poor wound healing of the perianal and perineal region. Moreover, the data suggest that 5-year survival after APR is only 40–70% [17], which points to a patient population with poor tumor biology necessitating an APR as salvage due to tumor recurrence or persistence after definitive CMT.

The treatment of SCCA requires a multidisciplinary approach and should involve medical, radiation, and surgical oncology. Since chemoradiation became the treatment standard of care, only a few randomized clinical trials have been performed (Table 10.3) [18–24]. The current recommendation for management of locally advanced SCCA is a combination of 5-fluorouracil (5-FU) and concurrent radiation therapy, with mitomycin C (MMC) or alternatively cisplatin.

Although in RTOG 98-11, the patient group that had MMC as a cytotoxic agent experienced favorable outcomes compared to cisplatin (5-year progression-free survival [PFS], overall survival [OS], and colostomy-free survival [CFS]; $p < 0.05$), the results do not reflect the actual comparison results due to two facts: (1) the investigational arm not only evaluated the role of induction chemotherapy but

Table 10.3 Randomized clinical trials for combined modulation therapy (CMT) for squamous cell carcinoma of anal canal (SCCA)

Study	Methods	Findings
RTOG 87–04/ECOG [18]	Objective: comparison between 5-FU + RT and 5-FU/MMC + RT	4-year colostomy rates: 13.0% less for the mitomycin group, $p = 0.002$ Colostomy-free survival at 4 years = 12.0% higher for mitomycin group, $p = 0.014$ PFS at 4 years = 22.0% higher for mitomycin group, $p = 0.0003$
ACT I [19]	Objective: comparison between radiation therapy (RT) versus chemoradiation (5-FU /MMC+ RT)	12-year: 25.3% reduction for chemoradiation arm (CI = 17.5–32.5 fewer) 12-year mortality: 12.5% reduction for chemoradiation arm (CI = 4.3–19.7 fewer)
EORTC [20]	Objective: Comparison between radiation therapy (RT) and chemoradiation with 5-FU / MMC + RT	5-year local control rate: 50.0% (RT) versus 68.0% (chemoradiation), $p = 0.02$ 5-year colostomy-free rate: 40.0% (RT) versus 72.0% (chemoradiation), $p = 0.002$ 5-year PFS: Chemoradiation resulted in improved, $p = 0.05$ 5-year OS: $p = 0.17$
RTOG 98-11 [21, 22]	Objective: comparison between concurrent 5-FU/MMC + RT and induction 5-FU/cisplatin, then concurrent 5-FU /cisplatin + RT	5-year PFS: 10.0% higher for MMC group, $p = 0.006$ 5-year OS: 7.6% higher for MMC group Colostomy-free survival: significant for MMC group, $p = 0.05$
ACCORD 03 [23]	Objective: comparison among ICT (induction chemotherapy: 5FU/cisplatin) + RCT of standard dose, ICT + RCT of higher dose, RCT of standard dose, and RCT of higher dose	No statistical differences were observed among the treatment groups in terms of 5-year CFS (colostomy-free survival), LC (local recurrence), or TFS (tumor free survival); $p > 0.05$
ACT II [24]	Objective: Direct comparison between 5-FU/MMC + RT versus 5-FU/cisplatin + RT	Complete response at 26 weeks: no statistical difference between MMC and cisplatin group, $p = 0.64$ 3-year Colostomy-free rate: no statistical difference between MMC and cisplatin group, $p = 0.26$ 3-year PFS for maintenance versus no maintenance: no statistical difference, $p = 0.70$

5-FU 5-fluorouracil, *MMC* mitomycin C, *RT* radiation therapy, *PFS* progression-free survival

also the role of cisplatin: (2) in the cisplatin arm, there was a delay on the initiation of chemoradiation [22].

Unfortunately, the only study listed in Table 10.3 that directly compared MMC to cisplatin was ACT II, in patients with locally advanced SCCA [24]. The last update showed no statistical significance for CR (complete response) between the MMC and cisplatin groups (90.5% vs. 89.5%, a difference of only around 1.0%, CI = −4.9–3.1, $p = 0.64$). Additionally, the results showed similar toxicity profiles for the study groups. However, the study did not achieve its primary end point, which was to demonstrate that 5-FU/MMC was superior to 5-FU/cisplatin. As a result, the standard of care for concurrent 5-FU/MMC remains unchanged.

The outcomes of cisplatin-based chemoradiation were analyzed by Eng et al. [25]. In this retrospective study of 201 patients with locally advanced SCCA, the patients received weekly (20 mg/m^2) or daily (4 mg/m^2) cisplatin added to a 5-FU-based regimen and a median radiation dose of 55 Gy. The study showed a recurrence rate of 11.0% after a median follow-up of 8.6 years and favorable 5-year survival outcomes (disease-free survival [DFS]: 81.0%, OS: 86.0%, and CFS: 88.0%). Thus, the authors concluded that cisplatin could be an alternative to MMC in the combination chemoradiation therapy for locally advanced SCCA.

Radiation options include both external and internal radiation. External radiation techniques include external beam radiation therapy (EBRT) consisting of three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT). Internal radiation involves brachytherapy. Inguinal nodes should be included in the treatment field even if they are not clinically or pathologically proven positive. Usually external radiation is given concurrently with chemoradiation for 5 days a week for 5–6 weeks. As a standard of practice in the United States, major hospitals and cancer centers are delivering IMRT targeting cancerous tissues with higher intensity, while at the same time minimizing adjacent normal tissues to lower intensity of radiation. Studies found that IMRT is associated with a low rate of toxicities, along with satisfactory local control, PFS, and OS [26, 27].

Like IMRT, brachytherapy can also deliver high-dose radiation to the main tumor while sparing the surrounding normal tissues. The iridium-192 (Ir-192) isotope is commonly used in brachytherapy. Although it plays an important role in local radiation dose escalation, it has limitations. It is suggested that no more than 50% of the circumference should be implanted and the maximum longitudinal length should not exceed 5 cm [27].

Consideration of the addition of biologic agent(s) for locally advanced SCCA is not currently well established. Based on molecular analysis, SCCA shows the expression of EGFR (epidermal growth factor receptor) like the other squamous cell carcinomas of the body [28]. Several studies (ACCORD 16 and Olivatto et al) [29, 30] have shown promising reports for cetuximab, but eventually noticed severe adverse effects. These studies included cisplatin in combination with chemoradiation. Phase II clinical trials have assessed the tolerability of anti-EGFR therapy during the standard concurrent chemoradiation (for cetuximab: ECOG 3205, NCT01621217; for panitumumab: NCT01285778, NCT01843452, NCT01581840; and for nimotuzumab: NCT01382745) [31].

Recently, cancer immunotherapy has also been evolving. For locally advanced SCCA, a phase II trial evaluating ADXS11–001 in combination radiation therapy (5-FU/MMC and IMRT) is currently recruiting participants (NCT01671488).

Metastatic

Of all SCCA patients, 20–30% will develop metastatic disease. The liver is the primary site for metastasis of SCCA. The recommendation for treatment depends on the previous treatment, duration of disease-free period, and the performance status. As metastatic disease is considered a rare event, consensus is lacking for the standard of care treatment. Currently, palliative chemotherapy with or without radiation is widely practiced for metastatic SCCA in the United States. Both National Comprehensive Cancer Network (NCCN) and European guidelines suggest cisplatin and 5-FU as first-line therapy agents with an overall response rate of about 60.0% and a median survival of about 12 months [32–37].

Overall, there is a lack of well-established peer-reviewed data for stage IV SCCA, with a majority of reports being anecdotal cases and case cohorts [38–40]. Among them, the most favorable outcomes were observed in phase I study by Hainsworth et al. [39]. They evaluated paclitaxel, carboplatin, and continuous infusional 5-FU in patients with other solid tumors with concurrent metastatic SCCA. The authors found that the anal subgroup ($n = 5$) had a median duration of response of 26 months.

We have published the largest retrospective study evaluating the outcomes of systemic chemotherapy for patients with metastatic SCCA who had received either 5-FU/cisplatin or carboplatin/paclitaxel [41]. That study concluded that a multidisciplinary approach in selected patients with metastatic SCCA effectively improved survival.

The first prospective randomized phase II trial for metastatic SCAA is the InterAACT (International Multicenter Study in Advanced Anal Cancer), which is currently recruiting participants (https://clinicaltrials.gov/ct2/show/NCT02051868). The study is designed to compare outcomes between 5-FU/cisplatin and carboplatin/paclitaxel combinations for patients with metastatic SCCA.

Very few studies have demonstrated the role of targeted therapy for metastatic SCCA, but no recommendation has been established [42, 43]. Cancer immunotherapy agents for

metastatic SCCA are being tested on trials currently. A phase II study (NCT02426892) at MD Anderson has been completed in order to evaluate the role of the PD-1 antibody, nivolumab, in refractory metastatic SCCA. The study has stopped accrual and the final results are expected to be presented in late 2018.

Locally Recurrent

Salvage abdominoperineal resection (APR) is reserved for locally persistent, progressive, or recurrent SCCA. Salvage surgery demands an extensive perineal resection, often requiring complex perineal reconstruction with myocutaneous flaps for wound coverage; however, patients still have met with significant complications [44–47]. According to the European Society for Medical Oncology (ESMO), salvage surgery demonstrates favorable local control (about 60.0% cases) and a 5-year survival rate (30–60%).

HIV-Positive Patients

The incidence of SCCA in HIV+ patients in the United States started to increase in the early 1990s. Between 1992 and 2003, the rate increased from 19.0 to 78.2 per 100,000 person-years [48]. It is believed that HIV+ patients develop SCCA due to high rates of HPV co-infection (2–6 times higher than that of the general population) [8].

It was noticeable in some reports that HIV+ patients with SCCA receiving highly active anti-retroviral therapy (HAART) did worse than HIV patients [49–52]. Importantly, HIV+ patients on HAART required a longer treatment duration, exhibited more toxicities, and developed more local recurrences, while displaying worse treatment responses.

Although increased toxicity and poor tolerance are two major concerns for HIV+ patients having SCCA, they should receive HAART with standard combination therapy to improve CD4 levels. The CD4 count plays an important role in the treatment decision tree as it has been shown that patients with a CD4 count greater than 200 have better treatment tolerance [53, 54].

Patients with SCCA who are HIV+ should be evaluated for baseline CD4 count before starting treatment and establish care with an infectious disease specialist to assist in creating a treatment strategy by the primary medical oncologist. The aim should promote HAART compliance and assess for toxicity during regular evaluation of the treatment.

Finally, cancer immunotherapy in HIV+ patients by agents targeting programmed cell death (PD-1; nivolumab) and cytotoxic T-lymphocyte antigen 4 (CLTA-4: ipilimumab) is also on trial (NCT02408861).

Complications

Hematological complications (neutropenia, anemia, and thrombocytopenia) are major concerns during CMT, especially with MMC-containing regimen. Weekly blood counts should be performed. Other reported acute adverse effects besides nausea and vomiting include infection, stomatitis, diarrhea, and radiation dermatitis.

The principle short-term complications due to radiation are temporary anal irritation, pain, skin changes, and common gastrointestinal symptoms such as nausea and diarrhea.

In both males and females, the long-term radiation treatment may cause permanent destruction of anal tissue leading to scarring, weakening of bone and blood vessels resulting in fractures and rectal bleeding, chronic proctitis, anal stenosis causing incontinent anal sphincter, nonhealing perineal ulcers, and infertility.

In females, an additional delayed anatomical complication due to radiation is vaginal stenosis leading to dyspareunia. If the pelvic radiation treatment plan includes the ovaries, pre-menopausal women should be counseled on the high possibility of future infertility.

Surveillance

SCCA is typically radiation-sensitive but can regresses at a slow pace after completion of CMT taking up to 26 weeks [55].

Although not nationally standardized, a physical exam including a DRE with groin checks for inguinal lymphadenopathy should begin around 6–12 weeks of chemoradiation. For MD Anderson Cancer Center recommendations, please visit: https://www.mdanderson.org/education-and-research/resources-for-professionals/clinical-tools-and-resources/practice-algorithms/survivorship-anal-web-algorithm.pdf.

In addition to physical exams, a pelvic MRI, CT scan of the abdomen and pelvis, or PET-CT scan may be advised during surveillance, at the clinician's discretion. Transrectal ultrasound (TRUS) is controversial, as it is difficult to differentiate between edema or scar tissue and tumor post-treatment.

If the patient has complete response:

- DRE, anoscopy, and palpation of inguinal nodes should be performed every 3–6 months for 5 years.
- An additional 3 months of observation is recommended if the patient has persistent, but clinically regressing disease seen at the initial 3 months after CMT completion.
- Recurrent or progressive disease should be confirmed histologically before considering salvage surgery or other treatment options.

Biomarkers and Prognostic Factors

In general, biomarkers in cancer management may assist in the design of individualized therapy, and analyses of such markers have been evolving in recent years. Unfortunately, there are few studies available on profiling of biomarkers for SCCA. Multi-platform tumor profiling can identify important targets related to specific therapeutic options:

- KRAS and EGFR status may allow the consideration of cetuximab in combination therapy [29, 30, 56].
- EGFR and HER2 status may introduce options with trastuzumab in selected patients [57].
- Mutations of PIK3CA may target the downstream PIK3CA/Akt/mTOR pathway through biologic agents [57–59].

Studies have shown that patients with tumors that exhibit molecular overexpression of tumor suppressors p21 and p53 are associated with lower overall survival rate and higher locoregional failure [60, 61]. However, clinical prognostic indicators including tumor size (≥5 cm), nodal involvement, and male gender are associated with inferior outcomes [62].

Prevention

Avoidance of preventable risk factors, mainly through safe sexual practices, are absolute necessities to prevent HPV-related anal precancerous lesions and subsequent SCCA. Although safe sexual practices are important, they are not perfectly followed and HPV-related disease may ultimately prevail. A more effective means of HPV-related disease prevention – US Food and Drug Administration (FDA)-approved – is the HPV vaccine that prevents certain types of HPV infections.

Vaccines approved for SCCA prevention include:

- Gardasil (recombinant HPV quadrivalent vaccine): approved for both females and males aged between 9 and 26 for the prevention of HPV (6, 11, 16, and 18) related anal cancers, and precancerous anal lesions.
- Gardasil 9 (recombinant HPV nonavalent vaccine): approved for both females and males aged between 9 and 26 for the prevention of HPV-related SCCA (6, 11, 16, 18, 31, 33, 45, 52, 58) and precancerous anal lesions.

Though most of the efficacy data on HPV vaccines comes from the cohorts with HIV-patients, there are only a few reports available for HIV+ patients. Three completed studies showed that in HIV+ patients HPV vaccines were immunogenic and well tolerated [63–65]. At the time of the writing of this chapter, there have been ongoing studies evaluating HPV vaccines on HIV+ patients (NCT01209325, NCT01031069, NCT00941889, and NCT01461096).

Conclusion

Combined modality therapy is the mainstay of treatment for SCCA, with surgery reserved only as salvage for recurrent or persistent diseases not cured by CMT. Other non-SCCA are treated like rectal cancer.

Female patients should be counseled on possible sexual dysfunction due to pelvic irradiation, and infertility if applicable.

HIV+ patients should continue HAART during standard CMT and have a baseline CD4 count evaluation.

HPV prevention is pivotal to reduce the incidence of SCCA, and the HPV vaccination is advised for both men and women at the appropriate ages.

Finally, every SCCA should be evaluated carefully, treated individually, and complicated cases should employ a multidisciplinary treatment strategy.

References

1. National Cancer Institue N. Seer stat fact sheets: Anal cancer. 2015 [cited 2015 10/15/2015]; Available from: http://seer.cancer.gov/statfacts/html/anus.html.
2. Tseng CJ, Liang CC, Soong YK, Pao CC. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. Obstet Gynecol. 1998;91(1):92–6.
3. Melbye M, Rabkin C, Frisch M, Biggar RJ. Changing patterns of anal cancer incidence in the United States, 1940–1989. Am J Epidemiol. 1994;139(8):772–80.
4. Palefsky JM, Holly EA, Hogeboom CJ, Ralston ML, DaCosta MM, Botts R, et al. Virologic, immunologic, and clinical parameters in the incidence and progression of anal squamous intraepithelial lesions in hiv-positive and hiv-negative homosexual men. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;17(4):314–9.
5. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer. 2004;101(2):270–80.
6. Frisch M, Glimelius B, van den Brule AJ, Wohlfahrt J, Meijer CJ, Walboomers JM, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med. 1997;337(19):1350–8.
7. van der Zee RP, Richel O, de Vries HJ, Prins JM. The increasing incidence of anal cancer: can it be explained by trends in risk groups? Neth J Med. 2013;71(8):401–11.
8. Dandapani SV, Eaton M, Thomas CR Jr, Pagnini PG. Hiv- positive anal cancer: an update for the clinician. J Gastrointest Oncol. 2010;1(1):34–44.
9. Nordenvall C, Nilsson PJ, Ye W, Nyren O. Smoking, snus use and risk of right- and left-sided colon, rectal and anal cancer: a 37-year follow-up study. Int J Cancer. 2011;128(1):157–65.
10. Wise PE. Anal cancer expanded version 2016. Available from: https://www.fascrs.org/patients/disease-condition/anal-cancer-expanded-version.
11. Eng C. Anal canal cancers, an issue of surgical oncology clinics of North America. 1st ed. Amsterdam, Netherlands: Elsevier; 2016.
12. Pineda CE, Welton ML. Management of anal squamous intraepithelial lesions. Clin Colon Rectal Surg. 2009;22(2):94–101.
13. Burgos J, Curran A, Tallada N, Guelar A, Navarro J, Landolfi S, et al. Risk of progression to high-grade anal intraepithelial neoplasia in hiv-infected msm. AIDS. 2015;29(6):695–702.

14. Melbye M, Sprogel P. Aetiological parallel between anal cancer and cervical cancer. Lancet. 1991;338(8768):657–9.
15. Salit IE, Lytwyn A, Raboud J, Sano M, Chong S, Diong C, et al. The role of cytology (pap tests) and human papillomavirus testing in anal cancer screening. AIDS. 2010;24(9):1307–13.
16. American Joint Committee on Cancer. In: Amin MBES, Greene FL, Byrd DB, Brookland RK, Washington MK, et al., editors. Ajcc cancer staging manual. 8th ed. New York: Springer Nature; 2017.
17. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. N Engl J Med. 2000;342(11):792–800.
18. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol. 1996;14(9):2527–39.
19. Anonymous. Epidermoid anal cancer: results from the ukcccr randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Ukcccr anal cancer trial working party. Uk co-ordinating committee on cancer research. Lancet. 1996;348(9034):1049–54.
20. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the european organization for research and treatment of cancer radiotherapy and gastrointestinal cooperative groups. J Clin Oncol. 1997;15(5):2040–9.
21. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB 3rd, Thomas CR Jr, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA. 2008;299(16):1914–21.
22. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB 3rd, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012;30(35):4344–51.
23. Peiffert D, Tournier-Rangeard L, Gerard JP, Lemanski C, Francois E, Giovannini M, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized unicancer accord 03 trial. J Clin Oncol. 2012;30(16):1941–8.
24. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (act II): a randomised, phase 3, open-label, 2 × 2 factorial trial. Lancet Oncol. 2013;14(6):516–24.
25. Eng C, Chang GJ, You YN, Das P, Xing Y, Delclos M, et al. Long-term results of weekly/daily cisplatin-based chemoradiation for locally advanced squamous cell carcinoma of the anal canal. Cancer. 2013;119(21):3769–75.
26. Mitchell MP, Abboud M, Eng C, Beddar AS, Krishnan S, Delclos ME, et al. Intensity-modulated radiation therapy with concurrent chemotherapy for anal cancer: outcomes and toxicity. Am J Clin Oncol. 2014;37(5):461–6.
27. DeFoe SG, Beriwal S, Jones H, Rakfal S, Heron DE, Kabolizadeh P, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal carcinoma–clinical outcomes in a large national cancer institute-designated integrated cancer centre network. Clin Oncol. 2012;24(6):424–31.
28. Paliga AA, Onerheim R, Gologan A, Spatz A, Vuong T. Egfr expression in invasive anal carcinoma. In: 2011 Gastrointestinal cancers symposium. San Fransisco: ASCO University; 2011.
29. Deutsch E, Lemanski C, Paris E, Delarochefordiere A, Rio E, Miglianico L, et al. Cetuximab plus radiochemotherapy in locally advanced anal cancer: interim results of the French multicenter phase II trial accord16. J Clin Oncol. 2011;29:1.
30. Olivatto LO, Vieira FM, Pereira BV, Victorino AP, Bezerra M, Araujo CM, et al. Phase 1 study of cetuximab in combination with 5-fluorouracil, cisplatin, and radiotherapy in patients with locally advanced anal canal carcinoma. Cancer. 2013;119(16):2973–80.
31. Levy A, Azria D, Pignon JP, Delarochefordiere A, Martel-Lafay I, Rio E, et al. Low response rate after cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: long-term results of the unicancer accord 16 phase II trial. Radiother Oncol. 2015;114(3):415–6.
32. Faivre C, Rougier P, Ducreux M, Mitry E, Lusinchi A, Lasser P, et al. 5-fluorouracil and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer. 1999;86(10):861–5.
33. Jaiyesimi IA, Pazdur R. Cisplatin and 5-fluorouracil as salvage therapy for recurrent metastatic squamous cell carcinoma of the anal canal. Am J Clin Oncol. 1993;16(6):536–40.
34. Tanum G. Treatment of relapsing anal carcinoma. Acta Oncol. 1993;32(1):33–5.
35. Khater R, Frenay M, Bourry J, Milano G, Namer M. Cisplatin plus 5-fluorouracil in the treatment of metastatic anal squamous cell carcinoma: a report of two cases. Cancer Treat Rep. 1986;70(11):1345–6.
36. Ajani JA, Carrasco CH, Jackson DE, Wallace S. Combination of cisplatin plus fluoropyrimidine chemotherapy effective against liver metastases from carcinoma of the anal canal. Am J Med. 1989;87(2):221–4.
37. Kim R, Byer J, Fulp WJ, Mahipal A, Dinwoodie W, Shibata D. Carboplatin and paclitaxel treatment is effective in advanced anal cancer. Oncology. 2014;87(2):125–32.
38. Wilking N, Petrelli N, Herrera L, Mittelman A. Phase ii study of combination bleomycin, vincristine and high-dose methotrexate (bom) with leucovorin rescue in advanced squamous cell carcinoma of the anal canal. Cancer Chemother Pharmacol. 1985;15(3):300–2.
39. Hainsworth JD, Burris HA 3rd, Meluch AA, Baker MN, Morrissey LH, Greco FA. Paclitaxel, carboplatin, and long-term continuous infusion of 5-fluorouracil in the treatment of advanced squamous and other selected carcinomas: results of a phase II trial. Cancer. 2001;92(3):642–9.
40. Jhawer M, Mani S, Lefkopoulou M, Hahn RG, Harris J, Catalano PJ, et al. Phase II study of mitomycin-c, adriamycin, cisplatin (map) and bleomycin-ccnu in patients with advanced cancer of the anal canal: an eastern cooperative oncology group study e7282. Investig New Drugs. 2006;24(5):447–54.
41. Eng C, Rogers J, Chang GJ, You YN, Das P, Rodriguez-Bigas MA, et al. Choice of chemotherapy in the treatment of metastatic squamous cell carcinoma of the anal canal. J Clin Oncol. 2012;30(15_suppl):4060.
42. De Dosso S, Martin V, Zanellato E, Frattini M, Saletti P. Molecular characterization and response to cetuximab in a patient with refractory squamous cell anal carcinoma. Tumori. 2010;96(4):627–8.
43. Lukan N, Strobel P, Willer A, Kripp M, Dinter D, Mai S, et al. Cetuximab-based treatment of metastatic anal cancer: correlation of response with kras mutational status. Oncology. 2009;77(5):293–9.
44. Chessin DB, Hartley J, Cohen AM, Mazumdar M, Cordeiro P, Disa J, et al. Rectus flap reconstruction decreases perineal wound complications after pelvic chemoradiation and surgery: a cohort study. Ann Surg Oncol. 2005;12(2):104–10.
45. Butler CE, Gundeslioglu AO, Rodriguez-Bigas MA. Outcomes of immediate vertical rectus abdominis myocutaneous flap reconstruction for irradiated abdominoperineal resection defects. J Am Coll Surg. 2008;206(4):694–703.
46. Sunesen KG, Buntzen S, Tei T, Lindegaard JC, Norgaard M, Laurberg S. Perineal healing and survival after anal cancer salvage surgery: 10-year experience with primary perineal reconstruction using the vertical rectus abdominis myocutaneous (vram) flap. Ann Surg Oncol. 2009;16(1):68–77.

47. Lefevre JH, Parc Y, Kerneis S, Shields C, Touboul E, Chaouat M, et al. Abdomino-perineal resection for anal cancer: impact of a vertical rectus abdominis myocutaneous flap on survival, recurrence, morbidity, and wound healing. Ann Surg. 2009;250(5):707–11.
48. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among hiv-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med. 2008;148(10):728–36.
49. Oehler-Janne C, Huguet F, Provencher S, Seifert B, Negretti L, Riener MO, et al. Hiv-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of hiv-positive patients receiving highly active antiretroviral therapy. J Clin Oncol. 2008;26(15):2550–7.
50. Oehler-Janne C, Seifert B, Lutolf UM, Ciernik IF. Local tumor control and toxicity in hiv-associated anal carcinoma treated with radiotherapy in the era of antiretroviral therapy. Radiat Oncol. 2006;1:29.
51. Hogg ME, Popowich DA, Wang EC, Kiel KD, Stryker SJ, Halverson AL. Hiv and anal cancer outcomes: a single institution's experience. Dis Colon Rectum. 2009;52(5):891–7.
52. Kauh J, Koshy M, Gunthel C, Joyner MM, Landry J, Thomas CR Jr. Management of anal cancer in the hiv-positive population. Oncology (Williston Park). 2005;19(12):1634–8; discussion 1638–1640, 1645 passim.
53. Hoffman R, Welton ML, Klencke B, Weinberg V, Krieg R. The significance of pretreatment cd4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. Int J Radiat Oncol Biol Phys. 1999;44(1):127–31.
54. Place RJ, Gregorcyk SG, Huber PJ, Simmang CL. Outcome analysis of HIV-positive patients with anal squamous cell carcinoma. Dis Colon Rectum. 2001;44(4):506–12.
55. Glynne Jones R, James R, Meadows H, Begum R, Cunningham D, Lederman JA, et al. Optimum time to assess complete clinical response (cr) following chemoradiation (crt) using mitomycin (mmc) or cisplatin (cisp), with or without maintenance cisp/5fu in squamous cell carcinoma of the anus: results of act II. J Clin Oncol. 2012;30:4004.
56. Casadei Gardini A, Capelli L, Ulivi P, Giannini M, Freier E, Tamberi S, et al. Kras, braf and pik3ca status in squamous cell anal carcinoma (scac). PLoS One. 2014;9(3):e92071.
57. Smaglo BG, Tesfaye A, Halfdanarson TR, Meyer JE, Wang J, Gatalica Z, et al. Comprehensive multiplatform biomarker analysis of 199 anal squamous cell carcinomas. Oncotarget. 2015;6(41):43594–604.
58. Janku F, Hong DS, Fu S, Piha-Paul SA, Naing A, Falchook GS, et al. Assessing pik3ca and pten in early-phase trials with pi3k/akt/mtor inhibitors. Cell Rep. 2014;6(2):377–87.
59. Millis SZ, Ikeda S, Arguello D, Feldman R, Maney RT, Xiu J, et al. Pi3k/pten/akt/mtor pathway aberrations and co-incidence of hormone receptors and her2 in 19,784 diverse solid tumors. In: 2015 ASCO annual meeting. Chicago: ASCO University; 2015.
60. Holm R, Skovlund E, Skomedal H, Florenes VA, Tanum G. Reduced expression of p21waf1 is an indicator of malignant behaviour in anal carcinomas. Histopathology. 2001;39(1):43–9.
61. Bonin SR, Pajak TF, Russell AH, Coia LR, Paris KJ, Flam MS, et al. Overexpression of p53 protein and outcome of patients treated with chemoradiation for carcinoma of the anal canal: a report of randomized trial RTOG 87–04. Radiation therapy oncology group. Cancer. 1999;85(6):1226–33.
62. Chin YJ, Hong ST, Wo JY. Anal cancer: current and future treatment strategies. Gastrointest Cancer. 2013;3:19–27.
63. Levin MJ, Moscicki AB, Song LY, Fenton T, Meyer WA 3rd, Read JS, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in hiv-infected children 7 to 12 years old. J Acquir Immune Defic Syndr. 2010;55(2):197–204.
64. Centers for Disease C, Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males–advisory committee on immunization practices (acip), 2011. MMWR Morb Mortal Wkly Rep. 2011;60(50):1705–8.
65. Mascolini M. Quadrivalent hpv vaccine elicits antibody and cell responses in hiv+ teens, young adults. In: 20th international AIDS conference. Melbourne: NATAP; 2014.

Cholangiocarcinoma

11

Daniel H. Ahn and Tanios Bekaii-Saab

Introduction

Biliary tract cancers (BTCs) are a rare and heterogeneous group of tumors that arise from the neoplastic proliferation of cholangiocytes or epithelium of the biliary tract. They are divided into three subgroups including intrahepatic cholangiocarcinoma (IHCC), extrahepatic cholangiocarcinoma (EHCC), and cancer of the gallbladder (Fig. 11.1). While all three anatomic subsets fall under BTC, our increased understanding of the heterogeneity that these entities exhibit helps classify them as distinct entities, with differences in both recurrence patterns and prognosis. Additionally, immunohistochemical studies revealed phenotypic traits of cholangiocytes and progenitor cells consistent with their anatomic sites of origin [1]. Progenitor cells from the canals of Hering and those within the peribiliary glands have been identified in intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma and gallbladder cancers, respectively [1–4]. While BTCs are treated uniformly, molecular and genomics of the cancer suggest that these differences should establish more individualized treatment approaches.

Epidemiology

BTCs are often considered an orphan group of malignancies due to their rarity, accounting for only 3% of all gastrointestinal malignancies [5]. However, despite its relative infrequency in comparison to other solid tumor malignancies, BTC accounts for approximately 13% of cancer-related deaths worldwide. Over the past several decades, there is a rise in the incidence and cancer-related deaths in BTC [6].

With the exception of known risk factors (e.g., parasitic infectious etiologies [7–13] and primary sclerosing cholangitis [14]), the vast majority of cases of BTC are idiopathic, with no clear identifiable risk factors. However, the rise in incidence in BTC may be attributable to the increasing prevalence of hepatitis C infection, as well as other chronic inflammatory hepatic diseases (cholecystitis, fatty liver disease, obesity) [7–13].

Diagnosis and Treatment

Prominent signs and symptoms at presentation include abnormal liver function tests, abdominal discomfort, weight loss, and jaundice. BTC is diagnosed with a combination of testing, including laboratory tests, imaging, and endoscopic procedures.

The Role of Adjuvant Therapy in Early-Stage Disease

Approximately 30–40% of patients diagnosed with biliary cancer present with early-stage disease where surgical resection, the only potential curative therapy, is the treatment of choice [15, 16]. Despite an improvement in surgical approaches, the curative rate is low, with high rates and differing patterns of initial recurrence after surgical resection [17]. Gallbladder cancers presented with distant metastatic disease in approximately 85% of patients upon recurrence, whereas 60% of cholangiocarcinoma patients present primarily with locoregional pattern upon disease recurrence [17]. These findings affirm that biliary tract cancers are a heterogeneous group of diseases with varying recurrence patterns and this may require differing approaches with adjuvant therapy.

While the role for adjuvant therapy is established in other gastrointestinal (GI) malignancies, notably colon and pancreas cancer [18, 19], the clinical benefit in biliary cancers is unknown due to the lack of randomized clinical trials. Existing data is poor, whereby the studies are retrospective in nature, based off single institutional experiences or are

D. H. Ahn · T. Bekaii-Saab (✉)
Division of Hematology/Medical Oncology, Mayo Clinic, Phoenix, AZ, USA
e-mail: Bekaii-Saab.Tanios@mayo.edu

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_11

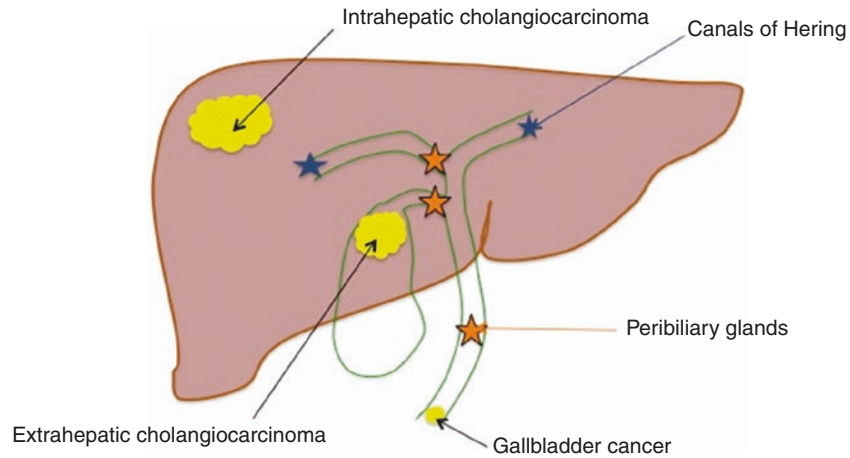


Fig. 11.1 Diagram of the sites of origin of primary biliary tract cancer. The figure visually depicts the three primary biliary tract cancers: intrahepatic and extrahepatic cholangiocarcinomas and gallbladder cancers. The stars represent progenitor cells of origin. (orange, peribiliary glands; blue, canals of Hering)

comprised of a very heterogeneous disease population. This has resulted in no consensus on the benefits or type of adjuvant therapy following resection in BTC. While the paucity of data has led to the absence of a consensus for adjuvant treatment, several studies suggest that certain adverse risk factors are associated with survival, primarily lymph node (LN) involvement, tumor number, and vascular invasion [20].

A large meta-analysis of 20 studies evaluated the role of adjuvant therapy (including chemotherapy, radiotherapy, and chemoradiation) compared to curative-intent surgery alone in patients with primary biliary tract cancer (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer). Patients with LN-positive disease (OR 0.49; $p = 0.004$) or those who had a R1 resection (evidence of microscopic disease within 0.1 cm of the surgical margin) (OR 0.36; $p = 0.002$) derived the greatest benefit from adjuvant therapy [21]. Additionally, patients who received adjuvant chemotherapy or concurrent chemoradiation derived a greater clinical benefit than radiotherapy alone. While acknowledging the limitations of retrospective analyses, patients with LN-positive disease or R1 resection could be considered for adjuvant therapy following surgical resection. Recently, a multicenter single-arm phase II study SWOG S0809 examined the role of adjuvant therapy in extrahepatic cholangiocarcinoma and gallbladder carcinoma in patients with adverse risk features (pT2-T4, LN-positive or positive resection margins) [22]. Patients received chemotherapy (four cycles of either gemcitabine or capecitabine) followed by concurrent chemoradiation. The treatment regimen was well tolerated with minimal significant adverse effects, and patients experienced a median overall survival of 35 months [22]. While this did not include primary intrahepatic cholangiocarcinoma, these findings suggest adjuvant therapy is safe, well tolerated, and may provide a clinical benefit in patients with biliary cancer.

Current ongoing phase III trials will provide further clarity for the clinical benefit of adjuvant therapy in this disease (Table 11.1).

Table 11.1 Current phase III trials for adjuvant therapy in biliary cancer

Country	Treatment	Disease[a]	Phase
UK	Capecitabine versus observation	GB, IHCC, EHCC	III
France	Gemcitabine + oxaliplatin versus observation	GB, IHCC, EHCC	III
Germany/UK	Gemcitabine + cisplatin versus observation	GB, IHCC, EHCC	III
Japan	S-1 versus observation	GB, IHCC, EHCC	III

[a]*GB* gallbladder, *IHCC* intrahepatic cholangiocarcinoma, *EHCC* extrahepatic cholangiocarcinoma

The Role of Liver Transplantation in Locally Advanced Unresectable Biliary Tract Cancers

Orthotopic liver transplantation (OLT) for unresectable BTC is often a relative contraindication to poor long-term outcomes and high rates of relapse. However, improvement in surgical techniques and stringent criteria led to improved 5-year survival rates and lower posttransplantation tumor recurrence [23]. Based off these improvements, the Mayo Clinic developed a protocol that entailed strict patient selection criteria, limiting OLT to patients with unresectable cholangiocarcinoma above the cystic duct without intrahepatic or extrahepatic metastases [24]. Patients received neoadjuvant concurrent chemoradiation, followed by brachytherapy with iridium and chemotherapy (5-fluorouracil) until transplantation. In their initial published case series, 11 out of 19 patients successfully underwent OLT, where all patients remained alive, with a median follow-up of 44 months. Based off these promising findings, OLT has been accepted by many institutions as a potential curative option for a select group of patients. A recent meta-analysis that included 14 American and European centers demonstrated an overall 5-year survival of 39%, where patients who received adjuvant chemoradiation experienced a 5-year survival that reached 57% [25]. However, several issues with OLT are seen including a high rate of non-compliance in patients with poor prognostic features, which include elevated

cancer antigen 19-9 (CA 19-9) levels, tumor diameters >3 cm, and Model for End-Stage Liver Disease (MELD) scores >20 [26]. Additionally, in a recently published report from a Mayo Clinic series, in approximately 50% of patients who underwent OLT, there was no evidence of malignancy in their post-resection liver specimen [27]. These findings may contribute to the lowered rates of recurrences and an improvement in long-term patient outcomes seen post OLT. Based on these findings, while OLT may be beneficial for select patients, the overall role for transplantation in BTC is unclear. Larger case series, including prospective randomized studies, are needed to validate its role as a curative treatment for BTC.

The Role of Cytotoxic Therapy in Advanced, Unresectable Biliary Cancer

At the time of diagnosis, the majority of patients present with advanced or metastatic disease, where treatment is palliative. Based on a large, randomized stage III trial conducted by Valle et al., the combination of gemcitabine and cisplatin chemotherapy has become a standard approach in treating advanced BTC. The combination demonstrated the superior clinical efficacy when compared to single-agent gemcitabine [28]. Patients who received the combination experienced a 3.6-month survival benefit in comparison to gemcitabine monotherapy with similar rates of adverse events. Although 80% of patients experienced tumor control, the vast majority of patients develop treatment resistance a few months after treatment, with a median progression free survival (PFS) that remains less than 1 year [28].

Patient outcomes in second-line therapies refractory to gemcitabine platinum-based therapy result in dismal outcomes, highlighting the need for novel and effective therapies in this disease (Table 11.2) [29–35].

Targeting Critical Signaling Pathways Involved in Biliary Tract Cancers

Recently, an increased understanding has altered the treatment in cancer by identifying and targeting signaling pathways integral to oncogenesis. Studies revealing a high incidence of genomic alterations in downstream signaling pathways involved in tumor proliferation, growth, and therapy resistance has led to an interest in developing novel targeted therapies against relevant downstream signaling pathways in BTC.

While initial trials that investigated novel, molecular targeted therapeutic agents demonstrated interesting antitumor activity in several patients, the overall results have been negative, with outcomes similar to chemotherapy agents in the refractory setting (Table 11.3) [36–48].

Table 11.2 Clinical trials for patients refractory to gemcitabine/platinum combination therapy in advanced BTC

Author	Treatment	Phase	# of pts	PFS[a]	OS[a]	ORR (%)
He [29]	FOLFOX-4	II	37	3.1	NR	21.6
Paule [30]	Gemcitabine/Oxaliplatin + Cetuximab	II	9	4	7	22
Sasaki [35]	Irinotecan	II	13	1.8	6.7	7.7
Suzuki [31]	S-1	II	40	2.5	6.8	7.5
Croitoru [33]	Gemcitabine/5-FU	II	17	3.2	13.2	17.6

Pts patients, *PFS* progression-free survival, *OS* overall survival, *ORR* overall response rate
[a]In months

Table 11.3 Results from clinical trials with select molecularly targeted agents

Author	Treatment	Target	pts in refractory setting (%)	PFS[a]	OS[a]	ORR (%)
Bekaii-Saab [36]	Selumetinib	MEK	39	3.7	9.8	12
Finn [38]	Binimetinib	MEK	43	2.14	4.78	7
Ahn [39]	MK-2206	Akt	100	0.5–6.6	2.2–20.2	0
Ramanathan [40]	Lapatinib	HER-2	65	1.8	5.2	0
Peck [37]	Lapatinib	HER-2	100	2.6	5.1	0
Philip [41]	Erlotinib	EGFR	57	2.6[a]	7.6	8
Lubner [42]	Erlotinib + bevacizumab	EGFR + VEGFR	0	4.4a	9.9	11
El-Khoueiry [44]	Sorafenib	VEGFR, PDGFR, RAF	0	3	9	0
Bengala [45]	Sorafenib	VEGFR, PDGFR, RAF	56	2.3	4.4	2
El-Khoueiry [43]	Erlotinib + Sorafenib	EGFR, VEGFR, PDGFR, RAF	0	2	6	6
Yi [46]	Sunitinib	VEGFR, PDGFR, RET	100	1.7[a]	4.8	8.9
Buzzoni [47]	Everolimus	mTOR	100	3.2	7.7	5.1
Santoro [48]	Vadentanib	VEGF, EGFR, RET	0	105[b]	228[b]	2

Pts patients, *PFS* progression free survival, *OS* overall survival, *ORR* overall response rate
EGFR epidermal growth factor receptor, *VEGFR* vascular endothelial growth factor receptor, *mTOR* mammalian target of rapamycin
[a]In months
[b]In days

This may be in part due to a nonselected patient population, where patients are eligible for enrollment regardless of their tumor genomic alterations. Furthermore, the ability to accrue a sufficient number of patients in a timely manner in clinical trials has led to allowing all anatomic groups into its eligibility, which may result in differing outcomes given our understanding of the different groups within biliary cancer.

Through new technologies, recent studies have allowed us to better understand the genomic landscape and its prognostic role in biliary tract cancer, as well as identify molecular alterations that may be potential therapeutic targets in this disease. While studies have identified common mutations across all anatomic groups (gallbladder cancers, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma), certain targetable mutations that are enriched mostly in IHCC suggest differing influences in pathogenesis and reinforcing that biliary cancer encompasses a spectrum of different, heterogeneous diseases. Herein, we will provide an overview of novel genomic variants that are of interest as potential therapies in BTC.

Targeting the Vascular Endothelial Growth Factor (VEGF) Pathway in Biliary Tract Cancers

Vascular endothelial growth factor (VEGF) promotes tumor proliferation in many malignancies including BTCs. In addition to angiogenesis and vascular permeability, VEGF also facilitates signaling in tumor cells [49]. It is highly expressed in up to 75% of BTCs and is associated with a more aggressive phenotype and poor prognosis [50].

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that binds to and neutralizes all human VEGF-A. This agent was first introduced into clinical trials in the 1990s. Phase I studies suggested that bevacizumab as a single agent was safe and relatively nontoxic and its combination with cytotoxic chemotherapy did not seem to exacerbate chemotherapy-related toxicities [51, 52]. Its activity has been validated in several solid tumor malignancies in the advanced setting, including colorectal cancer. In several phase II studies, bevacizumab in combination with chemotherapy and erlotinib failed to demonstrate any clinical improvement, resulting in similar outcomes seen with the standard therapies [42, 53].

Cediranib

In addition to VEGF, its receptors, VEGFR1 and VEGFR2, are aberrantly overexpressed in adjacent endothelial cells of the biliary tract, suggesting that it may be a relevant therapeutic target in BTC [54]. Cediranib is a multi-target small molecule inhibitor of VEGFR (VEGFR1–3), platelet-derived growth factor receptors (PDGFR), and c-Kit [55]. Given the association between angiogenesis and prognosis in BTC, Valle et al. conducted a randomized, 2-arm phase II study examining the addition of cediranib to combination gemcitabine and cisplatin chemotherapy, with progression-free survival (PFS) being its primary endpoint. While the combination demonstrated higher rates of tumor control (78% vs 65%), no significant difference in PFS was seen in comparison to the control arm (8 months in the cediranib group and 7.4 months in the placebo group, $p = 0.72$).

Sorafenib

Sorafenib is a multi-target small molecule inhibitor with activity against VEGFR, platelet-derived growth factor receptor-beta (PDGFR-β[beta]), and RAF kinases. In hepatocellular and renal cell carcinoma, sorafenib has been shown to be effective with meaningful clinical activity and have become standardized therapies. This benefit, however, has not translated in BTC. As a single agent, sorafenib showed minimal antitumor activity in BTC, with 0–2% response rates and a median PFS of only 2.3–3 months in BTC [44, 45]. Other trials have evaluated sorafenib in combination with cytotoxic chemotherapy, which failed to demonstrate any benefit with gemcitabine or in combination with gemcitabine and cisplatin [56, 57].

Sunitinib

Sunitinib is a multi-target small molecule inhibitor that targets VEGF, PDGFR, c-KIT, and RET. While it has been shown to be effective in gastrointestinal malignancies, including gastrointestinal stromal tumors and pancreatic neuroendocrine carcinoma [58, 59], the clinical activity has not been seen in BTC. A single-arm phase II study by Yi et al. examined the role of sunitinib as a second-line therapy in refractory BTC [46]. The study showed a median time to progression of 1.7 months and an objective response rate of 8.9% and 50% disease control rate, with tolerable adverse effects [46]. Sunitinib was safe and tolerable in patients with advanced BTC but marginal clinical activity was seen with this agent in this disease.

Vandetanib

Vandetanib is a multi-target small molecule inhibitor with activity against VEGF, epidermal growth factor receptor (EGFR), and RET. Its activity in BTC was assessed in a three-treatment arm, phase II study in treatment-naïve patients with BTC, where patients were randomized to receive vandetanib monotherapy, vandetanib in combination with gemcitabine, or gemcitabine with placebo. No significant differences in patient outcomes were seen with vandetanib monotherapy or in combination with gemcitabine compared to single-agent gemcitabine [48].

Thus, therapies targeting VEGF including monoclonal antibodies against VEGF (bevacizumab) or multi-targeted small molecule inhibitors with activity against VEGF have failed to demonstrate any significant clinical activity in randomized clinical trials in BTC [42, 48, 53, 56, 60]. The absence of predictive biomarkers may have contributed to the lack of clinical activity seen from VEGF-targeted agents, resulting in a dampened interest in these therapies in BTC. If a prognostic or predictive biomarker is identified, this may enrich the patient population likely to benefit from VEGF-targeted agents, resulting in a renewed interest into investigating their therapeutic role in the treatment of BTC.

Targeting the Epidermal Growth Factor Receptor (EGFR) Pathway in Biliary Tract Cancers

EGFR is often aberrantly overexpressed in all three anatomic groups in BTC [61–63]. This signaling pathway is important in biliary epithelial cell growth and proliferation, where EGFR overexpression has been associated with a poor prognosis and increased risk for tumor progression and invasion [64, 65]. The preclinical activity and its efficacy in other cancers have provided the rationale for targeting the EGFR pathway in BTC [66].

Erlotinib

Erlotinib is a reversible small molecule inhibitor of EGFR. Based on its efficacy in other solid tumor malignancies – notably lung, head and neck cancers – several phase II studies have been completed in BTC. Philip et al. conducted a single-arm phase II trial in patients with advanced refractory BTC, where all patients received erlotinib 150 mg orally twice daily [41]. A median PFS of 2.6 months and median overall survival (OS) of 7.5 months was seen in patients who participated in the trial. Despite 81% of patients having EGFR expression in their tumor samples, only three patients experienced a clinical response [41]. Given the association of EGFR overexpression and angiogenesis with patient outcomes in BTC, a single-arm phase II study was conducted to investigate the combination of erlotinib with bevacizumab in advanced BTC [42]. Six patients (12%) experienced a partial response and another 25 (51%) patients experienced stable disease. A time to progression of 4.4 months and a median OS of 9.9 months was observed, similar to historical controls [42].

A phase III study was conducted to assess the clinical efficacy of erlotinib in combination with chemotherapy (gemcitabine and oxaliplatin) in the first-line setting in advanced BTC [67]. Patients were randomized in a 1:1 fashion to receive chemotherapy with or without erlotinib. No significant difference was seen between the two treatment groups in PFS or OS. Erlotinib, as a single agent, or in combination with targeted agents or chemotherapy failed to demonstrate any meaningful activity over historical standards seen in BTC.

Cetuximab and Panitumumab

Cetuximab is a monoclonal antibody that targets EGFR with demonstrated efficacy in several solid tumor malignancies including colorectal, lung, head and neck cancers. Early studies in BTC showed promising activity with an objective response rate of 63%, [68] including three patients who experienced a complete response. Based on this interesting clinical activity, a randomized phase II trial (BINGO) investigated the combination of gemcitabine and oxaliplatin with or without cetuximab [69]. The results of the trial were disappointing, with similar response rates and overall outcomes in both treatment arms failing to confirm the promising activity seen in earlier studies. Mutational status of KRAS and BRAF or EGFR overexpression was not prognostic of patient outcomes [69].

Panitumumab, a fully humanized monoclonal antibody that targets EGFR, has also been evaluated in the treatment in BTC. Studies in colorectal cancers have demonstrated efficacy of anti-EGFR therapies in KRAS wild-type tumors. Based off these results, Hezel et al. evaluated panitumumab in combination with gemcitabine and oxaliplatin in KRAS wild-type metastatic BTC. The study resulted in a response rate of 45%, with a median PFS of 10.6 months and median OS of 20.3 months. Additional trials that investigated various chemotherapy regimens in combination with panitumumab demonstrated similar findings, resulting in a larger randomized phase II study investigating the combination of gemcitabine and oxaliplatin with or without panitumumab. Similar to the BINGO trial, no significant difference was seen with the addition of panitumumab despite selecting for patients with *KRAS* wild-type tumors.

The absence of significant clinical activity from the addition of monoclonal antibodies targeting EGFR may be related to additional unidentified RAS mutations that may limit the antitumor activity of this class of agents in BTC. Recent studies have identified an additional 10% of other RAS mutations in colorectal cancer, where patients whose tumors harbored non-exon 2 *KRAS* mutant and *NRAS* mutations did not benefit from the addition of anti-EGFR therapy in combination with various chemotherapy regimens across several different settings [70–72]. Ongoing efforts to assess the genomic landscape in BTC may identify biomarkers predictive of response to anti-EGFR therapies, where improved patient selection may result in a benefit with anti-EGFR therapy. However, at this time, there is no role for this class of agents in the treatment of BTC.

Targeting Downstream Signaling Pathways in Biliary Tract Cancers

Mitogen-Activated Pathway

Preclinical studies have demonstrated constitutive aberrant activity of the mitogen-activated protein kinase (MAPK) pathway, where the growth of malignant cholangiocytes is dependent on p38 MAPK activity [73]. The MAPK pathway is activated by extracellular signals, including growth factor receptors and cytokines, where its activation results in the phosphorylation and downstream activation through RAS, RAF, MEK, and ERK. Phosphorylated ERK (pERK) transfers to the nucleus to affect cellular processes including tumor growth, proliferation, and treatment resistance in BTC. The high incidence of BRAF and KRAS mutations in preclinical studies suggests that inhibiting the MAPK pathway represents an intriguing therapeutic target in this disease [74].

Based off this rationale, several single-agent MEK inhibitors have undergone investigation in BTC. Bekaii-Saab et al. conducted a multicenter phase II study with selumetinib, a noncompetitive inhibitor of MEK 1/2 in patients with advanced BTC, where the primary endpoint was response rate [36]. In this study, three patients experienced a clinical response, including one complete response, and 68% of patients experienced stable disease [36]. Median PFS was 3.7 months and median OS was 9.8 months. BRAF V600E and KRAS mutations did not correlate with clinical response [36]. Binimetinib (MEK162), a second-generation noncompetitive inhibitor of MEK 1/2, was investigated in phase I trials in a similar patient population with advanced BTC. Similar findings were observed, with 2 out of 26 patients experiencing a clinical response and 46% of patients experiencing stable disease [75]. An expanded tumor mutational analysis, which assessed for PIK3CA, PTEN, MET, and KRAS failed to identify any association between tumor somatic variants and clinical response [75]. Thus, while MEK inhibitors demonstrated interesting antitumor activity in a small proportion of patients with BTC, larger randomized trials are needed to confirm those results.

Phosphatidylinositol 3-Kinase (PI3K/Akt) Pathway

The PI3k/Akt pathway is integral for cell proliferation and apoptosis. Deregulation of this pathway has been identified in BTC and has been associated with the development, invasiveness, and treatment resistance in BTC. Several studies have been conducted with agents targeting downstream effectors in the PI3K pathway in BTC. A phase II study investigated the efficacy of everolimus, an inhibitor of mTOR in patients with advanced, treatment-refractory BTC. A median PFS of 3.2 months and OS of 7.7 months was seen in patients who received everolimus, with an overall response rate of 5.1% [47]. A multicenter phase II study was conducted with MK-2206, an allosteric inhibitor of Akt in patients with BTC. While the trial was terminated prior to completion, no clinical responses were observed in the eight patients enrolled in the study [39]. The lack of activity seen with MEK and PI3K pathway inhibition may be a result of the dysregulation of multiple downstream signaling pathways that is often seen in malignancies. The targeted inhibition of a single signaling pathway results in the communication and upregulation of alternate signaling pathways. Preclinical studies have found the PI3K/Akt and MAPK pathway are often constitutively co-activated in BTC [76–81]. Combined targeted agents against relevant, multiple signaling pathways may be an alternate, effective strategy to increase clinical efficacy of downstream pathway inhibition in BTC.

Unveiling the Genomic Landscape and the Identification of Novel, Targetable Tumor Somatic Variants in Biliary Tract Cancers

The development and application of new technologies has enabled us to conduct comprehensive genomic profiling in many solid tumor malignancies to allow us to understand the genomic landscape of these diseases, including BTC. Importantly, these efforts have identified novel molecular alterations that may be targeted with novel therapies, holding promise in improving patient outcomes. Herein, we will provide an overview of these recent discoveries that should result in the development of a tailored, personalized approach for each individualized patient.

Human Growth Factor Receptor 2 (HER-2/Neu)

HER-2 (*HER-2/neu* or *ERBB2*) is an oncogene encoded by the *ERBB2* gene that is a member of the human epidermal growth factor receptor family. Its amplification or overexpression has been identified as an oncogenic driver in several solid tumor malignancies, and therapies that target *HER-2* have become a standardized approach in the treatment of breast and gastric cancer [82–84]. Studies evaluating *HER-2* overexpression in BTC have identified alterations in *HER-2* in gallbladder (about 10%) and extrahepatic cholangiocarcinomas (up to 25%), and have been associated with a more aggressive phenotype [85, 86]. While initial small case series demonstrated antitumor activity with anti-*HER-2*-directed therapy in BTC, this did not translate to an improvement in patient outcomes in clinical trials [37, 40, 87, 88]. The lack of clinical activity may be a result from a nonselected patient population, where patient eligibility was not based on *HER-2* status. The utilization of combined anti-HER-2 therapies and

a selected patient population based on HER-2 status may improve clinical efficacy and renew interest in HER-2 as therapeutic target in BTC.

BRAF V600E

As previously described, the *MAPK* pathway is integral in tumor proliferation and survival and antitumor therapy resistance and is often constitutively activated in BTC. Mutation of the *BRAF* gene can result in the activation of the MAPK pathway and has been identified as an oncogenic driver in several malignancies including colorectal cancer, melanoma, and non-small-cell lung carcinoma [89–92]. The most common *BRAF* mutation is V600E, where the mutation is a single amino acid substitution of valine from glutamic acid. In BTC, BRAFV600E occurs in approximately 3% of IHCC, where its presence has been associated with a poor prognosis [93, 94]. Small molecule inhibitors against *BRAF* have demonstrated antitumor activity in several malignancies and have become the standardized treatment for BRAF V600E-mutated metastatic melanoma [95–98]. Based off these findings, ongoing studies are investigating the therapeutic relevance from BRAF inhibition in other solid malignancies including BTC (Table 11.4).

Isocitrate Dehydrogenase (IDH) 1/2

IDH1 and *IDH2* encode metabolic enzymes that convert isocitrate into α(alpha)-ketoglutarate. Mutations in *IDH1/2* result in aberrant reduction of α(alpha)-ketoglutarate to 2-hydroxyglutarate, an "oncometabolite" that inhibits enzymatic activity dependent on α(alpha)-ketoglutarate, which regulates many processes including cell development, differentiation, and proliferation. Studies have identified *IDH* alterations as an integral component in the cholangiocarcinogenesis, where their mutations inhibit hepatocyte differentiation, resulting in the formation and proliferation of premalignant biliary lesions [99]. Agents targeting *IDH1* and *IDH2* are under investigation through clinical trials for tumors harboring *IDH1* and *IDH2* alterations (Table 11.4).

Fibroblast Growth Factor Receptor (FRGR)

Fibroblast growth factor receptors (FGFR1, 2, 3, and 4) are tyrosine kinase receptors that bind to fibroblast growth factors (FGFs) at their extracellular domain [100]. Several *FGFR2* chromosomal fusions (*FGFR2-PPHLN1, FGFR2-BICC1, FGFR2-TACC3, FGFR2-AHCYL1*) have been identified specifically in IHCC, where genomic assessments suggest an incidence upward of 50% in this anatomic subgroup [101–106]. Upon its fusion, the activation of the *FGFR2* receptor results in the autophosphorylation and activation of its downstream signaling pathways, including the *MAPK*, *PI3K/Akt*, and STAT pathways – all which regulate important cellular processes [107].

Small reported case series have demonstrated interesting antitumor activity from targeting *FGFR* in IHCC that exhibit *FGFR2* fusions, suggesting it to be a rationale therapeutic target. The results from ongoing phase II studies examining therapies aimed at targeting *FGFR2* mutant tumors will help in determining the role of *FGFR* inhibition in the treatment of BTC (Table 11.4).

ROS1 Fusions

ROS1 fusions occur in upward of 10% of IHCC [108]. In preclinical BTC studies, inactivation of *ROS1* gene resulted in tumor regression, suggesting the gene to play an important role in oncogenesis [109]. In non-small-cell lung adenocarcinoma, the inhibition of *ROS1* has been validated as a

Table 11.4 Ongoing clinical trials with select molecularly targeted agents

Target	Agent	Trial design (Phase)	NCT No.	Misc
IDH1	AG-120	Phase I	02073994	Tumors harboring IDH1 mutations with failure of prior standard therapy
IDH2	AG-221	Phase I/II	02273739	Tumors harboring IDH2 mutations including glioma and angioimmunoblastic T-cell lymphoma
FGFR2	BGJ398	Phase II	02150967	FGFR2 fusions or other FGFR mutations; limited to BTC
	Ponatinib		0226341	FGFR2 fusions; not limited to BTC
EGFR or VEGR	Panitumumab or bevacizumab with chemotherapy	Phase II	01206049	*KRAS* wild type
ALK/ ROS1	LDK378	Phase II	02374489	ROS1 or ALK overexpression
BRAF + MEK	Dabrafenib + Trametinib	Phase II	02034110	BRAF V600E-mutated cancers; not limited to BTC

EGFR epidermal growth factor receptor, *FGFR* fibroblast growth factor receptor, *IDH* isocitrate dehydrogenase

therapeutic target, reaffirming that targeting *ROS1* may be a potential treatment for IHCC patients who express *ROS1* alterations [110]. Prospective studies are needed to validate its role as an effective treatment option in this disease.

Notch Pathway

The Notch signaling pathway is integral in embryogenesis and structural development of the liver, where its dysregulation has been identified as a contributory mechanism in the pathogenesis of BTC. Preclinical work has shown that increased *NOTCH1* expression resulted in the development of IHCC, suggesting it to be important in tumor development and proliferation [111]. The upregulation of NOTCH receptors have been identified in primary hepatobiliary malignancies, including primary hepatocellular carcinoma (HCC), all anatomic groups of BTC, and in up to 80% of IHCC in early studies [112, 113]. Interestingly, a RAS-driven animal mouse model demonstrated that inhibition of specific NOTCH receptors led to the development of primary biliary cancer-like tumors while their inhibition resulted in the formation of primary HCC-like tumors [114]. From these findings, NOTCH pathway inhibition may represent a potential effective treatment in BTC. However, validation through prospective clinical trials is needed to understand the sequelae from its inhibition and to validate its antitumor activity in humans.

The Role of Immunotherapy for Biliary Tract Cancers

While strides in immunotherapy with other solid tumor malignancies have been made – notably melanoma, renal cell carcinoma, prostate cancer, and recently lung cancer – the role for immunotherapy in BTC is unknown. Tumors suppress an immune response through inducing tolerance in tumor-specific T cells by expressing ligands that bind to inhibitory receptors, or immune "checkpoints" on tumor-specific T cells that dampen their response against tumors. Therapies including antibodies aimed at inhibitory checkpoints on activated T cells – including cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1) and its binding ligand on tumor cells, programmed death ligand 1 (PD-L1) – have generated responses in several gastrointestinal malignancies, including BTC, in early-phase studies.

In a phase II study, 17 participants with non-colorectal mismatch repair (MMR)-deficient gastrointestinal malignancies received pembrolizumab, a PD-1 inhibitor, where an objective response rate was 47% [115]. Among the responders, four patients achieved a complete response, including a BTC patient. In patients with mismatch repair-proficient tumors, no interesting clinical activity was seen, where no objective response rates were seen [115]. Patients with MMR-deficient tumors were found to have many tumor genomic alterations that are likely to produce neo-antigens that can be recognized by T cells, suggesting that checkpoint blockade, with PD-1/PDL-1 inhibition, could be an effective strategy with immunotherapy for patients who have MMR-deficient tumors. In patients with mismatch repair-proficient tumors, strategies to increase neo-antigens in mismatch proficient tumors that include combining cytotoxic therapies (e.g., chemotherapy, radiation therapy) with immune checkpoint inhibitors, where DNA damage may increase neo-antigens that may be recognized by the immune system, may result in improved efficacy with immunotherapeutic agents.

While immune checkpoint inhibitors are promising immunotherapeutic agents, strategies aimed at targeting the microenvironment represent another potential avenue for immunotherapy. Inflammatory cytokines that regulate the expansion of immunosuppressive cells that limit T or NK cell recognition tumor cells is produced and found in high concentrations in BTC. Combination strategies including agents that effect the tumor microenvironment, including small molecule inhibitors and vaccines, are under consideration for future trials.

References

1. Cardinale V, Carpino G, Reid L, Gaudio E, Alvaro D. Multiple cells of origin in cholangiocarcinoma underlie biological, epidemiological and clinical heterogeneity. World J Gastrointest Oncol. 2012;4(5):94–102.
2. Theise ND, Saxena R, Portmann BC, Thung SN, Yee H, Chiriboga L, et al. The canals of hering and hepatic stem cells in humans. Hepatology. 1999;30(6):1425–33.
3. Cardinale V, Wang Y, Carpino G, Cui CB, Gatto M, Rossi M, et al. Multipotent stem/progenitor cells in human biliary tree give rise to hepatocytes, cholangiocytes, and pancreatic islets. Hepatology. 2011;54(6):2159–72.
4. Carpino G, Cardinale V, Onori P, Franchitto A, Berloco PB, Rossi M, et al. Biliary tree stem/progenitor cells in glands of extrahepatic and intraheptic bile ducts: an anatomical in situ study yielding evidence of maturational lineages. J Anat. 2012;220(2):186–99.
5. Lazaridis KN, Gores GJ. Cholangiocarcinoma. Gastroenterology. 2005;128(6):1655–67.
6. Patel T. Worldwide trends in mortality from biliary tract malignancies. BMC Cancer. 2002;2:10.
7. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol. 2011;8(9):512–22.
8. Charbel H, Al-Kawas FH. Cholangiocarcinoma: epidemiology, risk factors, pathogenesis, and diagnosis. Curr Gastroenterol Rep. 2011;13(2):182–7.
9. Dickson PV, Behrman SW. Distal cholangiocarcinoma. Surg Clin North Am. 2014;94(2):325–42.
10. Razumilava N, Gores GJ. Classification, diagnosis, and management of cholangiocarcinoma. Clin Gastroenterol Hepatol. 2013;11(1):13–21.e11; quiz e13–14.

11. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet (London, England). 2014;383(9935):2168–79.
12. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology. 2013;145(6):1215–29.
13. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis. 2004;24(2):115–25.
14. Tsaitas C, Semertzidou A, Sinakos E. Update on inflammatory bowel disease in patients with primary sclerosing cholangitis. World J Hepatol. 2014;6(4):178–87.
15. Wade TP, Prasad CN, Virgo KS, Johnson FE. Experience with distal bile duct cancers in u.S. Veterans affairs hospitals: 1987–1991. J Surg Oncol. 1997;64(3):242–5.
16. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. N Engl J Med. 1999; 341(18):1368–78.
17. Jarnagin WR, Ruo L, Little SA, Klimstra D, D'Angelica M, DeMatteo RP, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer. 2003;98(8):1689–700.
18. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the conko-001 randomized trial. JAMA. 2013;310(14):1473–81.
19. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350(23):2343–51.
20. de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol. 2011;29(23):3140–5.
21. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol. 2012;30(16):1934–40.
22. Ben-Josef E, Guthrie KA, El-Khoueiry AB, Corless CL, Zalupski MM, Lowy AM, et al. Swog s0809: a phase ii intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol. 2015;33(24):2617–22.
23. Iwatsuki S, Todo S, Marsh JW, Madariaga JR, Lee RG, Dvorchik I, et al. Treatment of hilar cholangiocarcinoma (klatskin tumors) with hepatic resection or transplantation. J Am Coll Surg. 1998;187(4):358–64.
24. De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, et al. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transpl. 2000;6(3):309–16.
25. Gu J, Bai J, Shi X, Zhou J, Qiu Y, Wu Y, et al. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. Int J Cancer. 2012;130(9):2155–63.
26. Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 us centers. Gastroenterology. 2012;143(1):88–98 e83; quiz e14.
27. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg. 2005;242(3):451–8; discussion 458–461.
28. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81.
29. He S, Shen J, Sun X, Liu L, Dong J. A phase ii folfox-4 regimen as second-line treatment in advanced biliary tract cancer refractory to gemcitabine/cisplatin. J Chemother. 2014;26(4):243–7.
30. Paule B, Herelle MO, Rage E, Ducreux M, Adam R, Guettier C, et al. Cetuximab plus gemcitabine-oxaliplatin (gemox) in patients with refractory advanced intrahepatic cholangiocarcinomas. Oncology. 2007;72(1–2):105–10.
31. Suzuki E, Ikeda M, Okusaka T, Nakamori S, Ohkawa S, Nagakawa T, et al. A multicenter phase ii study of s-1 for gemcitabine-refractory biliary tract cancer. Cancer Chemother Pharmacol. 2013;71(5):1141–6.
32. Bridgewater J, Palmer D, Cunningham D, Iveson T, Gillmore R, Waters J, et al. Outcome of second-line chemotherapy for biliary tract cancer. Eur J Cancer. 2013;49(6):1511.
33. Croitoru A, Gramaticu I, Dinu I, Gheorghe L, Alexandrescu S, Buica F, et al. Fluoropyrimidines plus cisplatin versus gemcitabine/gemcitabine plus cisplatin in locally advanced and metastatic biliary tract carcinoma – a retrospective study. J Gastrointest Liver Dis: JGLD. 2012;21(3):277–84.
34. Fornaro L, Vivaldi C, Cereda S, Leone F, Aprile G, Lonardi S, et al. Second-line chemotherapy in advanced biliary cancer progressed to first-line platinum-gemcitabine combination: a multicenter survey and pooled analysis with published data. J Exp Clin Cancer Res: CR. 2015;34(1):156.
35. Sasaki T, Isayama H, Nakai Y, Takahara N, Satoh Y, Takai D, et al. A pilot study of salvage irinotecan monotherapy for advanced biliary tract cancer. Anticancer Res. 2013;33(6):2619–22.
36. Bekaii-Saab T, Phelps MA, Li X, Saji M, Goff L, Kauh JS, et al. Multi-institutional phase ii study of selumetinib in patients with metastatic biliary cancers. J Clin Oncol. 2011;29(17):2357–63.
37. Peck J, Wei L, Zalupski M, O'Neil B, Villalona Calero M, Bekaii-Saab T. Her2/neu may not be an interesting target in biliary cancers: results of an early phase ii study with lapatinib. Oncology. 2012;82(3):175–9.
38. Finn RS, Ahn DH, Javle MM, Tan BR Jr, Weekes CD, Bendell JC, Patnaik A, Khan GN, Laheru D, Chavira R, Christy-Bittel J, Barrett E, Sawyer MB, Bekaii-Saab TS. Phase 1b investigation of the MEK inhibitor binimetinib in patients with advanced or metastatic biliary tract cancer. Invest New Drugs. 2018;36(6):1037–43. https://doi.org/10.1007/s10637-018-0600-2. Epub 2018 May 22.
39. Ahn DH, Li J, Wei L, Doyle A, Marshall JL, Schaaf LJ, et al. Results of an abbreviated phase-ii study with the akt inhibitor mk-2206 in patients with advanced biliary cancer. Sci Rep. 2015;5:12122.
40. Ramanathan RK, Belani CP, Singh DA, Tanaka M, Lenz HJ, Yen Y, et al. A phase ii study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. Cancer Chemother Pharmacol. 2009;64(4):777–83.
41. Philip PA, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, et al. Phase ii study of erlotinib in patients with advanced biliary cancer. J Clin Oncol. 2006;24(19):3069–74.
42. Lubner SJ, Mahoney MR, Kolesar JL, Loconte NK, Kim GP, Pitot HC, et al. Report of a multicenter phase ii trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase ii consortium study. J Clin Oncol. 2010;28(21):3491–7.
43. El-Khoueiry AB, Rankin C, Siegel AB, Iqbal S, Gong IY, Micetich KC, et al. S0941: a phase 2 swog study of sorafenib and erlotinib in patients with advanced gallbladder carcinoma or cholangiocarcinoma. Br J Cancer. 2014;110(4):882–7.
44. El-Khoueiry AB, Rankin CJ, Ben-Josef E, Lenz HJ, Gold PJ, Hamilton RD, et al. Swog 0514: a phase ii study of sorafenib in patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma. Invest New Drugs. 2012;30(4):1646–51.

45. Bengala C, Bertolini F, Malavasi N, Boni C, Aitini E, Dealis C, et al. Sorafenib in patients with advanced biliary tract carcinoma: a phase ii trial. Br J Cancer. 2010;102(1):68–72.
46. Yi JH, Thongprasert S, Lee J, Doval DC, Park SH, Park JO, et al. A phase ii study of sunitinib as a second-line treatment in advanced biliary tract carcinoma: a multicentre, multinational study. Eur J Cancer. 2012;48(2):196–201.
47. Buzzoni R, Pusceddu S, Bajetta E, De Braud F, Platania M, Iannacone C, et al. Activity and safety of rad001 (everolimus) in patients affected by biliary tract cancer progressing after prior chemotherapy: a phase ii itmo study. Ann Oncol. 2014;25(8):1597–603.
48. Santoro A, Gebbia V, Pressiani T, Testa A, Personeni N, Arrivas Bajardi E, et al. A randomized, multicenter, phase ii study of vandetanib monotherapy versus vandetanib in combination with gemcitabine versus gemcitabine plus placebo in subjects with advanced biliary tract cancer: the vangogh study. Ann Oncol. 2015;26(3):542–7.
49. Goel HL, Mercurio AM. Vegf targets the tumour cell. Nat Rev Cancer. 2013;13(12):871–82.
50. Quan ZW, Wu K, Wang J, Shi W, Zhang Z, Merrell RC. Association of p53, p16, and vascular endothelial growth factor protein expressions with the prognosis and metastasis of gallbladder cancer. J Am Coll Surg. 2001;193(4):380–3.
51. Gordon MS, Margolin K, Talpaz M, Sledge GW Jr, Holmgren E, Benjamin R, et al. Phase i safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol. 2001;19(3):843–50.
52. Margolin K, Gordon MS, Holmgren E, Gaudreault J, Novotny W, Fyfe G, et al. Phase ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. J Clin Oncol. 2001;19(3):851–6.
53. Zhu AX, Meyerhardt JA, Blaszkowsky LS, Kambadakone AR, Muzikansky A, Zheng H, et al. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose pet with clinical outcome: a phase 2 study. Lancet Oncol. 2010;11(1):48–54.
54. Benckert C, Jonas S, Cramer T, Von Marschall Z, Schafer G, Peters M, et al. Transforming growth factor beta 1 stimulates vascular endothelial growth factor gene transcription in human cholangiocellular carcinoma cells. Cancer Res. 2003;63(5):1083–92.
55. Wedge SR, Kendrew J, Hennequin LF, Valentine PJ, Barry ST, Brave SR, et al. Azd2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res. 2005;65(10):4389–400.
56. Lee JK, Capanu M, O'Reilly EM, Ma J, Chou JF, Shia J, et al. A phase ii study of gemcitabine and cisplatin plus sorafenib in patients with advanced biliary adenocarcinomas. Br J Cancer. 2013;109(4):915–9.
57. Moehler M, Maderer A, Schimanski C, Kanzler S, Denzer U, Kolligs FT, et al. Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: a double-blind placebo-controlled multicentre phase ii aio study with biomarker and serum programme. Eur J Cancer. 2014;50(18):3125–35.
58. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet (London, England). 2006;368(9544):1329–38.
59. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(22):3584–90.
60. Valle JW, Wasan H, Lopes A, Backen AC, Palmer DH, Morris K, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (abc-03): a randomised phase 2 trial. Lancet Oncol. 2015;16(8):967–78.
61. Xu L, Hausmann M, Dietmaier W, Kellermeier S, Pesch T, Stieber-Gunckel M, et al. Expression of growth factor receptors and targeting of egfr in cholangiocarcinoma cell lines. BMC Cancer. 2010;10:302.
62. Yoon JH, Gwak GY, Lee HS, Bronk SF, Werneburg NW, Gores GJ. Enhanced epidermal growth factor receptor activation in human cholangiocarcinoma cells. J Hepatol. 2004;41(5):808–14.
63. Kaufman M, Mehrotra B, Limaye S, White S, Fuchs A, Lebowicz Y, et al. Egfr expression in gallbladder carcinoma in north america. Int J Med Sci. 2008;5(5):285–91.
64. Yoshikawa D, Ojima H, Iwasaki M, Hiraoka N, Kosuge T, Kasai S, et al. Clinicopathological and prognostic significance of egfr, vegf, and her2 expression in cholangiocarcinoma. Br J Cancer. 2008;98(2):418–25.
65. Zhou YM, Li YM, Cao N, Feng Y, Zeng F. Significance of expression of epidermal growth factor (egf) and its receptor (egfr) in chronic cholecystitis and gallbladder carcinoma. Ai zheng = Aizheng =Chin J Cancer. 2003;22(3):262–5.
66. Yoshikawa D, Ojima H, Kokubu A, Ochiya T, Kasai S, Hirohashi S, et al. Vandetanib (zd6474), an inhibitor of vegfr and egfr signalling, as a novel molecular-targeted therapy against cholangiocarcinoma. Br J Cancer. 2009;100(8):1257–66.
67. Lee J, Park SH, Chang HM, Kim JS, Choi HJ, Lee MA, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2012;13(2):181–8.
68. Gruenberger B, Schueller J, Heubrandtner U, Wrba F, Tamandl D, Kaczirek K, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. Lancet Oncol. 2010;11(12):1142–8.
69. Malka D, Cervera P, Foulon S, Trarbach T, de la Fouchardiere C, Boucher E, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (bingo): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol. 2014;15(8):819–28.
70. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-folfox4 treatment and ras mutations in colorectal cancer. N Engl J Med. 2013;369(11):1023–34.
71. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. Folfiri plus cetuximab versus folfiri plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (fire-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(10):1065–75.
72. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. Peak: A randomized, multicenter phase ii study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mfolfox6) or bevacizumab plus mfolfox6 in patients with previously untreated, unresectable, wild-type kras exon 2 metastatic colorectal cancer. J Clin Oncol. 2014;32(21):2240–7.
73. Tadlock L, Yamagiwa Y, Marienfeld C, Patel T. Double-stranded rna activates a p38 mapk-dependent cell survival program in biliary epithelia. Am J Physiol Gastrointest Liver Physiol. 2003;284(6):G924–32.
74. Tannapfel A, Sommerer F, Benicke M, Katalinic A, Uhlmann D, Witzigmann H, et al. Mutations of the braf gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut. 2003;52(5):706–12.
75. Finn RSJM, Tan BR, Weekes CD, et al. A phase i study of mek inhibitor mek162 (arry-438162) in patients with biliary tract cancer. J Clin Oncol. 2012;30:4s.. (suppl; abstr 220).

76. Schmitz KJ, Lang H, Wohlschlaeger J, Sotiropoulos GC, Reis H, Schmid KW, et al. Akt and erk1/2 signaling in intrahepatic cholangiocarcinoma. World J Gastroenterol. 2007;13(48):6470–7.
77. Chung JY, Hong SM, Choi BY, Cho H, Yu E, Hewitt SM. The expression of phospho-akt, phospho-mtor, and pten in extrahepatic cholangiocarcinoma. Clin Cancer Res. 2009;15(2):660–7.
78. Deshpande V, Nduaguba A, Zimmerman SM, Kehoe SM, Macconaill LE, Lauwers GY, et al. Mutational profiling reveals pik3ca mutations in gallbladder carcinoma. BMC Cancer. 2011;11:60.
79. Li Q, Yang Z. Expression of phospho-erk1/2 and pi3-k in benign and malignant gallbladder lesions and its clinical and pathological correlations. J Exp Clin Cancer Res: CR. 2009;28:65.
80. Tanno S, Yanagawa N, Habiro A, Koizumi K, Nakano Y, Osanai M, et al. Serine/threonine kinase akt is frequently activated in human bile duct cancer and is associated with increased radioresistance. Cancer Res. 2004;64(10):3486–90.
81. Yoon H, Min JK, Lee JW, Kim DG, Hong HJ. Acquisition of chemoresistance in intrahepatic cholangiocarcinoma cells by activation of akt and extracellular signal-regulated kinase (erk)1/2. Biochem Biophys Res Commun. 2011;405(3):333–7.
82. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for her2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783–91.
83. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of her2-positive advanced gastric or gastro-oesophageal junction cancer (toga): a phase 3, open-label, randomised controlled trial. Lancet (London, England). 2010;376(9742):687–97.
84. Janjigian YY, Werner D, Pauligk C, Steinmetz K, Kelsen DP, Jager E, et al. Prognosis of metastatic gastric and gastroesophageal junction cancer by her2 status: a european and USA international collaborative analysis. Ann Oncol. 2012;23(10):2656–62.
85. Kim HJ, Yoo TW, Park DI, Park JH, Cho YK, Sohn CI, et al. Gene amplification and protein overexpression of her-2/neu in human extrahepatic cholangiocarcinoma as detected by chromogenic in situ hybridization and immunohistochemistry: its prognostic implication in node-positive patients. Ann Oncol. 2007;18(5):892–7.
86. Pignochino Y, Sarotto I, Peraldo-Neia C, Penachioni JY, Cavalloni G, Migliardi G, et al. Targeting egfr/her2 pathways enhances the antiproliferative effect of gemcitabine in biliary tract and gallbladder carcinomas. BMC Cancer. 2010;10:631.
87. Javle M, Churi C, Kang HC, Shroff R, Janku F, Surapaneni R, et al. Her2/neu-directed therapy for biliary tract cancer. J Hematol Oncol. 2015;8:58.
88. Kawamoto T, Ishige K, Thomas M, Yamashita-Kashima Y, Shu S, Ishikura N, et al. Overexpression and gene amplification of egfr, her2, and her3 in biliary tract carcinomas, and the possibility for therapy with the her2-targeting antibody pertuzumab. J Gastroenterol. 2015;50(4):467–79.
89. Schindler G, Capper D, Meyer J, Janzarik W, Omran H, Herold-Mende C, et al. Analysis of braf v600e mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol. 2011;121(3):397–405.
90. Michaloglou C, Vredeveld LC, Mooi WJ, Peeper DS. Braf(e600) in benign and malignant human tumours. Oncogene. 2008;27(7):877–95.
91. Brose MS, Volpe P, Feldman M, Kumar M, Rishi I, Gerrero R, et al. Braf and ras mutations in human lung cancer and melanoma. Cancer Res. 2002;62(23):6997–7000.
92. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the braf gene in human cancer. Nature. 2002;417(6892):949–54.
93. Goeppert B, Frauenschuh L, Renner M, Roessler S, Stenzinger A, Klauschen F, et al. Braf v600e-specific immunohistochemistry reveals low mutation rates in biliary tract cancer and restriction to intrahepatic cholangiocarcinoma. Mod Pathol. 2014;27(7):1028–34.
94. Robertson S, Hyder O, Dodson R, Nayar SK, Poling J, Beierl K, et al. The frequency of kras and braf mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. Hum Pathol. 2013;44(12):2768–73.
95. Kim KB, Cabanillas ME, Lazar AJ, Williams MD, Sanders DL, Ilagan JL, et al. Clinical responses to vemurafenib in patients with metastatic papillary thyroid cancer harboring braf(v600e) mutation. Thyroid. 2013;23(10):1277–83.
96. Dietrich S, Glimm H, Andrulis M, von Kalle C, Ho AD, Zenz T. Braf inhibition in refractory hairy-cell leukemia. N Engl J Med. 2012;366(21):2038–40.
97. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in braf-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet (London, England). 2012;380(9839):358–65.
98. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in braf v600-mutant advanced melanoma treated with vemurafenib. N Engl J Med. 2012;366(8):707–14.
99. Saha SK, Parachoniak CA, Ghanta KS, Fitamant J, Ross KN, Najem MS, et al. Mutant idh inhibits hnf-4alpha to block hepatocyte differentiation and promote biliary cancer. Nature. 2014;513(7516):110–4.
100. Belov AA, Mohammadi M. Molecular mechanisms of fibroblast growth factor signaling in physiology and pathology. Cold Spring Harb Perspect Biol. 2013;5(6):1–23.
101. Borad MJ, Champion MD, Egan JB, Liang WS, Fonseca R, Bryce AH, et al. Integrated genomic characterization reveals novel, therapeutically relevant drug targets in fgfr and egfr pathways in sporadic intrahepatic cholangiocarcinoma. PLoS Genet. 2014;10(2):e1004135.
102. Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. Oncologist. 2014;19(3):235–42.
103. Sia D, Losic B, Moeini A, Cabellos L, Hao K, Revill K, et al. Massive parallel sequencing uncovers actionable fgfr2-pphln1 fusion and araf mutations in intrahepatic cholangiocarcinoma. Nat Commun. 2015;6:6087.
104. Arai Y, Totoki Y, Hosoda F, Shirota T, Hama N, Nakamura H, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology. 2014;59(4):1427–34.
105. Wu YM, Su F, Kalyana-Sundaram S, Khazanov N, Ateeq B, Cao X, et al. Identification of targetable fgfr gene fusions in diverse cancers. Cancer Discov. 2013;3(6):636–47.
106. Graham RP, Barr Fritcher EG, Pestova E, Schulz J, Sitailo LA, Vasmatzis G, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. Hum Pathol. 2014;45(8):1630–8.
107. Kouhara H, Hadari YR, Spivak-Kroizman T, Schilling J, Bar-Sagi D, Lax I, et al. A lipid-anchored grb2-binding protein that links fgf-receptor activation to the ras/mapk signaling pathway. Cell. 1997;89(5):693–702.
108. Gu TL, Deng X, Huang F, Tucker M, Crosby K, Rimkunas V, et al. Survey of tyrosine kinase signaling reveals ros kinase fusions in human cholangiocarcinoma. PLoS One. 2011;6(1):e15640.
109. Saborowski A, Saborowski M, Davare MA, Druker BJ, Klimstra DS, Lowe SW. Mouse model of intrahepatic cholangiocarcinoma validates fig-ros as a potent fusion oncogene and therapeutic target. Proc Natl Acad Sci U S A. 2013;110(48):19513–8.

110. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ros1-rearranged non-small-cell lung cancer. N Engl J Med. 2014;371(21):1963–71.
111. Zender S, Nickeleit I, Wuestefeld T, Sorensen I, Dauch D, Bozko P, et al. A critical role for notch signaling in the formation of cholangiocellular carcinomas. Cancer Cell. 2013;23(6):784–95.
112. Yoon HA, Noh MH, Kim BG, Han JS, Jang JS, Choi SR, et al. Clinicopathological significance of altered notch signaling in extrahepatic cholangiocarcinoma and gallbladder carcinoma. World J Gastroenterol. 2011;17(35):4023–30.
113. Wu WR, Shi XD, Zhang R, Zhu MS, Xu LB, Yu XH, et al. Clinicopathological significance of aberrant notch receptors in intrahepatic cholangiocarcinoma. Int J Clin Exp Pathol. 2014;7(6):3272–9.
114. Huntzicker EG, Hotzel K, Choy L, Che L, Ross J, Pau G, et al. Differential effects of targeting notch receptors in a mouse model of liver cancer. Hepatology. 2015;61(3):942–52.
115. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. Pd-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–20.

Gallbladder Cancer: Current and Emerging Therapies

12

Maria Diab and Philip A. Philip

Introduction

Despite its low prevalence, gallbladder carcinoma (GBC) represents one of the most lethal malignancies, with a 5-year survival of <10% [1]. Its poor prognosis is related in part to its advanced stage on presentation due to its relatively silent course and vague symptoms and in part due to the lack of biomarkers to screen high-risk patients and facilitate early diagnosis [2]. Patients in advanced stages may present with painless jaundice and constitutional symptoms (unintentional weight loss, night sweats) [3]; most tumors are discovered incidentally during cholelithiasis surgeries [2]. GBC represents the most common malignancy of the biliary tract [4]. Females appear to be at a higher risk compared to males [5]. GBC is relatively rare in the Western world but seems to have clusters in Asian countries [6]; nonetheless, its incidence is increasing in the United States [5]. In 2017, an estimated 11,740 new GBC and other extrahepatic biliary cancer cases (of which ~4000 are GBC) were expected to be diagnosed in the United States; 3830 of these patients will die due to disease [5]. The only potentially curable treatment is surgical resection, but only 10–30% of patients are amenable to that [4], and even after complete resection, rates of local and distant recurrence are high [7]. For patients with positive margins, recurrence is often locoregional; for those with negative margins, recurrence is typically distant [7].

Several risk factors have been linked to the development of GBC [8]. By and large, gallstones (GS) are the most important risk factors, present in almost 96% of patients with GBC [9]. A longer duration of gallstone disease (20 years or more) and larger GS size (a diameter of 3 centimeters or more) are associated with higher risk [10, 11]. Despite the increased risk with GS, however, prophylactic cholecystectomies are not indicated, as only 1–2% of GS patients develop GBC [12]. Porcelain gallbladder, a manifestation of chronic cholecystitis, is associated with GS and with a higher risk of developing GBC (2–3% will develop GBC) [13]. Gallbladder polyps are also associated with GS and a higher risk for GBC [14]. Cholecystectomy for polyps larger than 1 centimeter is advised [15]. Biliary cysts and anomalous pancreaticobiliary duct junction—two congenital abnormalities more common in the Asian population—are associated with a higher risk for GBC, even in the absence of GS [16, 17]. The risk of GBC with biliary cysts depends on age, with lower risk in younger patients (0.7% in patients younger than 10 years and up to 50% in older patients) [16]. Obesity, chronic inflammation, and chronic infections are established risk factors for GBC [18, 19]. In patients with primary sclerosing cholangitis, 56% of patients with detected gallbladder masses were found to have GBC [20]. Chronic *Salmonella* typhi carrier state was associated with an approximately sixfold increase in the risk of GBC compared to control [19]. The association with *Helicobacter* infection remains debatable [21]. Other environmental risk factors include tobacco use [22], alcohol consumption [23], and obesity and insulin resistance [24].

Pathogenesis

Gallbladder adenocarcinoma represents the most common histologic type of GBC, constituting 85–90% of cases [25], and will be the focus of this chapter. Rare types include squamous cell, adenosquamous, and neuroendocrine carcinoma [25]. The model for gallbladder carcinogenesis (evolution from premalignant lesion to invasive carcinoma) relies heavily on the well-established model in colorectal cancer [26, 27]. The majority of GBC cases arise from the malignant transformation of epithelium in the context of chronic inflammation [28], which causes chronic irritation of the mucosa and fosters an environment suitable for malignant transformation. Increases in inflammatory cytokines lead

M. Diab (✉)
Department of Oncology, Karmanos Cancer Institute, Detroit, MI, USA
e-mail: diabm@karmanos.org

P. A. Philip
Department of Oncology, Department of Pharmacology, Wayne State University, Karmanos Cancer Institute, Detroit, MI, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_12

to the overexpression of cyclooxygenase-2 (COX-2) and the epigenetic inhibition of tumor suppressor genes [29]. Mutations of *TP53* and mitochondrial DNA are commonly observed in the early stages of GBC and drive the transformation of normal epithelium into metaplastic cells [30]. Overexpression of COX-2 also drives tumor neoangiogenesis [31]. Intraepithelial neoplasia ensues, which is associated with the loss of heterozygosity at loci 3p and 8p [32] and the overexpression of human epidermal growth factor receptor 2 (*HER2*) [33]. This is followed by the development of carcinoma in situ, in which mutations of fragile histidine triad (*FHT*) and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) are observed, as well as the loss of heterozygosity at 9q, 18q, 22q, 5q, and 17p [26, 34, 35]. Finally, invasive carcinoma arises; this is believed to be driven by mutations in *KRAS* as well as the loss of heterozygosity at 9p, 13q, and 18q [26, 34]. It is important to note that the previous model applies to carcinomas associated with GS, not those arising on a background of adenomatous polyps nor associated with anomalous pancreaticobiliary duct junction (this is more common in Japan) [36]. For carcinomas arising from the latter two settings, a different profile of *KRAS* and *TP53* mutations has been observed [36].

Diagnostic Biomarkers

At this time, there is no standard test that is used to screen high-risk individuals or to confirm diagnosis in patients suspected of having GBC.

Several biomarkers have been studied in the diagnosis and prognosis of GBC [37–41]. In one study, serum CA242, CA125, and CA19-9 levels in patients with GBC were significantly higher when compared with those in the benign gallbladder disease and healthy control groups ($P < 0.01$) [40]. The highest sensitivity and specificity for single tumor marker were for CA19-9 (sensitivity of 71.7%) and CA125 (specificity of 98.7%) [40]. Diagnostic accuracy was improved by combining CA19-9, CA242, and CA125 (69.2%). Postoperative serum levels of those three markers were lower in patients who did not experience recurrence compared to those who did ($P < 0.01$) [40].

MicroRNAs (miRNAs) are small (19–25 nucleotides) noncoding ribonucleic acids that regulate gene expression through binding to imperfect complementary regions in the 3′ untranslated region of the target messenger RNA and inhibiting their translation or promoting their degradation and hence promoting carcinogenesis or tumor suppression [42]. They play important roles in cell differentiation, proliferation, and apoptosis [42]. Their differential expression compared to healthy and nonmalignant pathologies has been studied in several malignancies, including GBC [1]. Tumor-suppressing miRNAs are downregulated in GBC and include miRNA-34a [43], miRNA-218-5p [44], and miRNA-335 [45]. Oncogenic miRNAs upregulated in GBC include miRNA-21 [46], miRNA-20a [47], miRNA-155 [48], and miRNA-182 [49]. Development of therapies targeting oncogenic miRNAs could be promising.

Treatment

High-quality prospective trials for the medical management of GBC are scarce because of its rarity. Many studies include patients with GBC along with patients with other biliary malignancies. However, they are underpowered to allow for subgroup analyses to further delineate the effect of therapy based on specific anatomical sites within the biliary tree. Furthermore, with the advent of targeted therapies and the evidence that some targeted therapies have been beneficial in other malignancies, the need for trials evaluating the efficacy of such therapy, alone or in combination with conventional chemotherapy, is growing.

Resectable Disease

As stated earlier, the only potentially curable treatment is surgical resection [50]. GBC patients who have resectable disease are encouraged to enroll in clinical trials testing adjuvant systemic therapies when feasible. If participation in a clinical trial is not an option, patients with completely resected, stage pT2, or more tumors or those with node- or margin-positive disease may benefit from adjuvant therapy [51, 52]. There is no consensus on the optimal adjuvant approach, i.e., chemotherapy (CT) alone versus chemoradiation (CRT) with chemotherapy. The choices for chemotherapy alone include gemcitabine, fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine), or gemcitabine plus a fluoropyrimidine [53]. Treatment is usually given for 6 months following surgical resection.

Another approach is combining chemoradiotherapy (CRT) with 4 months of systemic CT. The benefit in overall survival (OS) from CT, alone or in combination with CRT, versus radiation therapy (RT) alone was elucidated in a systematic review (OR, 0.39, 0.61, and 0.98, respectively; $P = 0.02$); the greatest benefit in survival was seen in patients with LN-positive disease (OR, 0.49; $P = 0.004$) and R1 disease (OR, 0.36; $P = 0.002$) [54]. Whether adjuvant RT should be administered alone or with concurrent CT is still being debated. The phase II SWOG S0809 trial evaluated the benefit of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in patients with extrahepatic cholangiocarcinoma and 25 patients with GBC (19 patients had R0 and 6 had R1) [55]. The 2-year survival for all patients was 65% (95% CI, 53–74%), and it was 67%

and 60% in R0 and R1 patients, respectively. Median OS was 35 months (R0, 34 months; R1, 35 months). Local, distant, and combined relapses occurred in 14, 24, and 9 patients. Grade 3 and 4 adverse effects were observed in 52% and 11% of patients, respectively, and were mainly neutropenia (44%), hand-foot syndrome (11%), diarrhea (8%), lymphopenia (8%), and leukopenia (6%).

For resected GBC with negative margins, negative regional nodes, or carcinoma in situ, the current recommendations from the National Comprehensive Cancer Network (NCCN) are observation, fluoropyrimidine chemoradiation, or fluoropyrimidine- or gemcitabine-based chemotherapy [56]. For R1 and R2 GBC, as well as disease with positive regional nodes, the NCCN recommends fluoropyrimidine chemoradiation followed by fluoropyrimidine- or gemcitabine-based chemotherapy, or fluoropyrimidine- or gemcitabine-based chemotherapy only [56]. Prospective trials are needed to further shed light on the role of either adjuvant approaches for resected GBC [57].

Unresectable, Locally Advanced, and Metastatic Disease

Similar to the management of resectable disease, guidelines for treating patients with advanced disease that are based on randomized clinical trials are lacking [56]. Knox et al. evaluated the combination gemcitabine plus capecitabine for first-line therapy in locally advanced and metastatic biliary tract malignancy, including GBC patients [58]. The overall response rate was 31%, with a median progression-free survival (PFS) and overall survival (OS) of 7 and 14 months, respectively. The treatment was generally well tolerated. Similar results were reported by Riechelmann et al. for the same combination as first-line treatment of locally advanced disease [59]. In 2007, a pooled analysis of available trials showed that combining gemcitabine and a platinum resulted in higher response rates and a trend toward improved survival in advanced disease compared to other regimens, including fluoropyrimidine-based ones [60]. Subsequently, the phase III Advanced Biliary Cancer-02 (ABC-02) trial, one of the hallmark trials in the management of biliary tract malignancies, confirmed the superiority of the gemcitabine-cisplatin combination over gemcitabine alone for nonresectable, recurrent, and metastatic disease [61], with a median PFS of 8.0 versus 5.0 months, respectively, and a median OS of 11.7 versus 8.1 months, respectively [61]. There was a nonsignificant increase in grade 3–4 neutropenia in the gemcitabine-cisplatin arm; infection rates were similar between the two arms. Liver function was significantly worse in the gemcitabine-only arm compared to the combination arm, which might reflect better disease control with the combination arm [61].

However, the question remains as to the impact of treatment on survival compared to supportive care. The only trial that compared best supportive care (BSC) to chemotherapy—fluorouracil/leucovorin (FUFA) versus modified gemcitabine/oxaliplatin (mGEMOX)—reported better outcomes with GEMOX [62]. Median OS was 4.5, 4.6, and 9.5 months for the BSC, FUFA, and mGEMOX arms, respectively. Median PFS was 2.8, 3.5, and 8.5 months, respectively. For locally advanced, unresectable disease, another option is fluoropyrimidine-based chemoradiotherapy as one therapeutic option in addition to palliative chemotherapy [56], but the normal tissue surrounding the tumor may limit the dose of radiation administered.

Targeted Therapies

Multiple pathways are aberrantly expressed in GBC (Table 12.1) and play a role in carcinogenesis, such as fostering uncontrolled cell proliferation, evading apoptosis, angiogenesis, and invasion [28, 63–67]. Their expression and the benefit of their blockade in other malignancies render them potential therapies in GBC. The molecular signature of GBC differs from other biliary tumors. For instance, *KRAS* mutations are more common in cholangiocarcinomas than GBC [28]. On the other hand, aberrations in the fibroblast growth factor receptor 2 (FGFR2) and isocitrate

Table 12.1 Frequency of aberrant expression of specific pathways in GBC compared to intrahepatic and extrahepatic cholangiocarcinoma [28, 63–67]

Pathway	GBC	IHCC	EHCC
Growth factors/receptors			
EGFR	6–12%	3–27%	5–20%
HER2	16%	0–1%	0–8%
MET	5–74%	21–58%	0%
VEGF	55–63%	53%	59%
FGFR2	0%	13–20%	0–5%
IDH1/2	0%	23–28%	0–7%
RAS-RAF-MEK pathway			
KRAS	0–13%	5–54%	0–40%
BRAF	0–33%	0–21%	0–2%
MEK	Unknown	Unknown	Unknown
PI3K-AKT-mTOR pathway			
PI3K/PIK3CA	4–12%	0–9%	0%
AKT	0%	0–3%	0%
mTOR	47–64%	25–70%	40–65%

AKT Protein kinase B, *BRAF* proto-oncogene BRAF, *EGFR* epithelial growth factor receptor, *EHCC* extrahepatic cholangiocarcinoma, *FGFR2* fibroblast growth factor receptor 2, *HER2* human epidermal growth factor receptor 2, *IDH1/2* isocitrate dehydrogenase 1 and 2, *IHCC* intrahepatic cholangiocarcinoma, *KRAS* Kirsten rat sarcoma viral oncogene homolog, *MET* hepatocyte growth factor receptor, *MAPK* mitogen-activated protein kinase, *MEK* MAPK kinase, *mTOR* mammalian target of rapamycin, *PI3K* phosphoinositide 3-kinase, *VEGF* vascular endothelial growth factor

dehydrogenase 1 (IDH1) and IDH2 are typically not observed in GBC, while they are frequent in intrahepatic cholangiocarcinomas [63].

Several trials evaluated the role of targeted therapy in GBC. Unfortunately, the majority of these trials are underpowered and test the drugs in molecularly unselected patients. Therefore, larger trials are needed with the goal of selecting patients using biomarkers.

Inhibitors of Growth Factors and Their Receptors

Epidermal Growth Factor Receptor (EGFR) Inhibitors

Epidermal growth factor receptor (EGFR), a member of the ErbB family of receptors, is composed of an extracellular ligand-binding domain and an intracellular domain with tyrosine kinase activity. It is commonly activated in malignant cells [68]. Its activation promotes cell proliferation, angiogenesis, and evasion of apoptosis [68] and may be predictive of increased mortality in biliary tract malignancies [69]. Erlotinib is a tyrosine kinase inhibitor that prevents activation of EGFR through reversible blockade of its adenosine triphosphate binding site, resulting in its inability to activate downstream pathways such as RAS-RAF-MEK and PI3K-AKT-mTOR [70]. Erlotinib monotherapy showed some benefit in a phase II trial of a small number of patients with advanced disease [70]. However, adding erlotinib to gemcitabine and oxaliplatin (GEMOX) failed to improve OS, despite a slight improvement in PFS [71].

Cetuximab (CTX) and panitumumab (PTB) are two monoclonal antibodies against EGFR that have also been evaluated in GBC [72, 73]. They selectively block the extracellular ligand-binding domain of the receptor, thereby preventing its activation [73]. Gruenberger et al. evaluated the addition of CTX to GEMOX in a single-arm, phase II trial for patients with advanced disease [73]. Although 63% of the patients achieved response (3 patients had complete response and 16 had partial response), no survival benefit was observed [73]. Grade 3, but not Grade 4, adverse events were observed in 13 out of 30 patients and included rash, peripheral neuropathy, and thrombocytopenia [73]. The BINGO trial, another phase II trial combining CTX to GEMOX, randomized patients with advanced biliary tract malignancies (including GBC) to either received cetuximab or not [74]. Similar to the results of Gruenberger et al., adding CTX to chemotherapy did not improve survival (PFS for the CTX-GEMOX was 6.1 months compared to 5.5 months for the GEMOX arm; OS was 11.0 and 12.4 months, respectively, for the CTX-GEMOX and GEMOX arms) [74].

Hezel et al. reported some encouraging results with adding PTB to GEMOX [75]. In a single-arm, phase II trial of 31 previously untreated, unresectable, or metastatic *KRAS* wild-type biliary tract (including GBC), the response rate was 45%, and median PFS and OS were 10.6 and 20.3 months, respectively [75]. The most common grade 3/4 adverse events were anemia (26%), leukopenia (23%), fatigue (23%), neuropathy (16%), and rash (10%) [75]. The Vecti-BIL study, another phase II trial, randomized chemotherapy-naive patients with advanced, *KRAS* wild-type biliary tract malignancies (including 28 patients) to receive GEMOX with or without PTB [76]. No survival benefit was observed; median PFS was 5.3 and 4.4 months, respectively, for the PTB-GEMOX and GEMOX-only arms, and median OS was 9.9 and 10.2 months, respectively [76].

Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitors

HER2, another member of the ErbB family, also promotes cell growth, survival, and motility and might actually be a more potent activator of these pathways than other receptors [77]. Overexpression of HER2 is more common in GBC compared to tumors in other sites of the biliary tree [78] and to other gastrointestinal tumors [79]. Interestingly, its overexpression has been associated with favorable outcomes, and patients with overexpressed HER2 are less likely to have metastatic disease [80]. However, although its blockade has been beneficial in the treatment of other malignancies, namely, breast and gastric, the benefit from its blockade in GBC has been modest at best. Lapatinib, an oral, dual inhibitor of EGFR and HER2, was evaluated in patients with advanced biliary tract malignancies, including GBC [81]. Lapatinib monotherapy resulted in a median PFS and OS of 1.8 and 5.2 months, respectively [81]. Similar results were reported from other studies [82, 83].

Vascular Endothelial Growth Factor (VEGF) Inhibitors

Vascular endothelial growth factor (VEGF) is a potent promoter of angiogenesis [84] and is overexpressed in 55–63% of GBC [28]. Its expression correlates with positive surgical margins, metastases, and poor survival [28, 85]. Bevacizumab is a monoclonal antibody that binds VEGF and prevents it from activating its receptor VEGFR [86]. Zhu et al. evaluated the combination of bevacizumab with GEMOX in a phase II trial of advanced biliary cancer patients [86]. Response rate was 40%, and median PFS and OS were 7 and 12.7 months, respectively [86]. However, the study did not meet the predefined endpoint of improving 6-month PFS from 50% to 70% [86]. Another phase II evaluated the addition of bevacizumab to gemcitabine/

capecitabine in 50 patients with advanced biliary tract malignancies, including 11 patients with GBC [87]. Twelve patients had partial response, and 24 had stable disease [87]. Median PFS and OS were 8.1 and 10.2 months, respectively; patients with detected circulating tumor cells at baseline had lower median OS compared to those without (9.4 vs. 13.7 months; $P = 0.29$) [87].

Lubner et al. evaluated the role of dual blockade of VEGF and EGFR with bevacizumab and erlotinib in a phase II trial of advanced cholangiocarcinoma and GBC, but the combination did not improve survival compared to upfront chemotherapy [88]. Response rate was 63%, and median PFS and OS were 4.4 and 9.9 months, respectively [88]. Sorafenib, a multi-kinase inhibitor of VEGFR, among other targets such as platelet-derived growth factor and BRAF, has been evaluated in the setting of GBC as monotherapy [89] as well as combined to chemotherapy (gemcitabine-cisplatin [90] and capecitabine-oxaliplatin [91]), but it failed to improve survival.

MET Inhibitors

MET, also known as the scatter receptor, is activated by the hepatocyte growth factor (HGF) and stimulates the synthesis of VEGF and interleukin-8, eventually feeding angiogenesis [92]. It also promotes invasion of tumor cells by degrading intercellular junctions [92]. Its overexpression has been associated with poor prognosis [93]. To date, no trial has evaluated the role of its blockade in GBC.

Fibroblast Growth Factor Receptor 2 (FGFR2) Inhibitors

The fibroblast growth factor, through activation of its receptor (FGFR2), regulates cell proliferation, migration, and angiogenesis [94]. *FGFR2* gene fusions were observed in intrahepatic cholangiocarcinomas [95], and an FGFR2 inhibitor is being evaluated in the setting of advanced cholangiocarcinomas [96]. However, FGFR2 aberrations have not been observed in GBC [63]. At this time, no FGFR2 has been identified for GBC.

Inhibitors of the RAS-RAF-MEK-MAPK Pathway

The RAS-RAF-MEK-MAPK pathway is downstream of surface growth factor receptors and plays an important role in promoting cell proliferation as well as evading apoptosis, through interacting with cell-cycle regulating proteins, such as *p53*, *p16*, and *p21* [97]. Furthermore, the pathway's first component, *KRAS*, cross-stimulates the PI3K-AKT pathway in addition to its primary downstream signaling of the RAS-RAF-MEK-MAPK axis [97]. Although *KRAS* and *BRAF* mutation status has been implicated in other malignancies, they are not considered to be prognostic markers in biliary tract malignancies [69]. Selumetinib is a small molecule inhibitor of *MEK* that selectively binds to an allosteric regulatory site on *MEK* and prevents the protein from utilizing adenosine triphosphate [98]. Selumetinib monotherapy was evaluated in a phase II trial that included 28 patients with advanced biliary tract malignancies, 7 of whom had advanced GBC [98]. Three patients had confirmed objective response; median PFS and OS were 3.7 and 9.8 months, respectively [98]. Toxicities were mainly grade 1 and 2 and were most frequently rash and xerostomia; 4% of patients had grade 4 fatigue [98]. Notably, no $BRAF^{V600E}$ mutations were found in tumor tissues [98]. The phase Ib trial ABC-04 evaluated selumetinib in combination with gemcitabine and capecitabine for 13 patients with advanced biliary tract malignancies (3 patients with GBC) [99]. Three patients had a partial response and 5 stable disease. Median PFS was 6.4 months. Toxicities related to selumetinib were mostly grade 1 and 2 and related to edema and rash.

Inhibitors of the PI3K-AKT-mTOR Pathway

Similar to the RAS-RAF-MEK pathway, the PI3K-AKT-mTOR pathway is stimulated by various growth factors and plays a crucial role in evading apoptosis, likely through stimulating BCL-2 and blocking the activity of caspase-9 [100]. It also promotes progression through the cell cycle, facilitates angiogenesis [101], and regulates the production of matrix metalloproteinases, which are pivotal for local invasion [102]. One of the downstream components, the mammalian target of rapamycin (mTOR), potentiates cell proliferation and promotes angiogenesis *through* production of hypoxia-inducible factor [103]. Overactivation of mTOR is associated with shortened overall survival [104].

Everolimus, an mTOR kinase inhibitor, has been tested and is approved by the US Food and Drug Administration (FDA) for the treatment of a number of tumors, including pancreatic neuroendocrine tumors and renal cell carcinomas [105]. Everolimus was studied in combination with gemcitabine and cisplatin in a phase I trial for patients with unresectable solid tumors, including GBC [105]. None of the GBC patients had an objective response. Toxicities related to everolimus included hyperlipidemia. Combining an mTOR inhibitor with 5-FU [106] and MAPK inhibitor [107] showed promising results in preclinical studies. Table 12.2 lists ongoing trials in the management of GBC.

Table 12.2 Select ongoing trials for advanced GBC

Regimen	ClinicalTrials.gov identifier
First-line	
GEMOX versus XELOX	NCT01470443
Gemcitabine + cisplatin + Nab-paclitaxel	NCT02392637
Gemcitabine + cisplatin + Nab-paclitaxel	NCT02632305
Irinotecan + cisplatin versus gemcitabine + cisplatin	NCT01859728
Ramucirumab or merestinib or placebo plus cisplatin and gemcitabine	NCT02711553
Acelarin + cisplatin	NCT02351765
Durvalumab + tremelimumab + gemcitabine + cisplatin	NCT03046862
Varlitinib + gemcitabine + cisplatin	NCT02992340
ADH-1 + gemcitabine + cisplatin	NCT01825603
Second-line	
MEK162 + capecitabine	NCT02773459
FOLFOX	NCT01926236
Ramucirumab	NCT02520141
Sulfatinib	NCT02966821

XELOX Capecitabine/oxaliplatin, *FOLFOX* 5-fluorouracil/folinic acid/oxaliplatin

Conclusion

Gallbladder cancer is a rare malignancy that is associated with a poor prognosis because diagnosis is made at a late stage and because of the lack of effective systemic therapies. The most common histological type is adenocarcinoma. The only potentially curable treatment is surgical resection, but only a small portion of patients are resectable because the majority present with late stages of disease. Patients must always be encouraged to enroll in clinical trials. Patients with completely resected, stage pT2, or more tumors or those with node- or margin-positive disease may benefit from adjuvant therapy, which can be in the form of either chemotherapy alone or chemoradiation with or without chemotherapy. For patients with unresectable, locally advanced, or metastatic disease, treatment options include palliative chemotherapy (gemcitabine- or fluoropyrimidine-based) or fluoropyrimidine chemoradiation with or without palliative chemotherapy. A number of targeted therapies have been evaluated in the setting of advanced disease, but none are FDA approved. Higher impact trials are needed to further guide the management of this disease.

References

1. Yang G, Zhang L, Li R, Wang L. The role of micrornas in gallbladder cancer. Mol Clin Oncol. 2016;5(1):7–13.
2. Higuchi R, Ota T, Araida T, Kajiyama H, Yazawa T, Furukawa T, et al. Surgical approaches to advanced gallbladder cancer: a 40-year single-institution study of prognostic factors and resectability. Ann Surg Oncol. 2014;21(13):4308–16.
3. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol. 2014;6:99–109.
4. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. Lancet Oncol. 2003;4(3):167–76.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
6. Zatonski WA, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB, Ghadirian P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the search program of the international agency for research on cancer. J Natl Cancer Inst. 1997;89(15):1132–8.
7. Silva MA, Tekin K, Aytekin F, Bramhall SR, Buckels JA, Mirza DF. Surgery for hilar cholangiocarcinoma; a 10 year experience of a tertiary referral centre in the UK. Eur J Surg Oncol. 2005;31(5):533–9.
8. Liebe R, Milkiewicz P, Krawczyk M, Bonfrate L, Portincasa P, Krawczyk M. Modifiable factors and genetic predisposition associated with gallbladder cancer. A concise review. J Gastrointestin Liver Dis. 2015;24(3):339–48.
9. Cariati A, Piromalli E, Cetta F. Gallbladder cancers: associated conditions, histological types, prognosis, and prevention. Eur J Gastroenterol Hepatol. 2014;26(5):562–9.
10. Andrea C, Enzo A. Cholesterol gallstones larger than 3 cm appear to be associated with gallbladder cancer: identification of a high risk group of patients that could benefit from preventive cholecystectomy. Ann Surg. 2016;263(3):e56.
11. Zatonski WA, La Vecchia C, Przewozniak K, Maisonneuve P, Lowenfels AB, Boyle P. Risk factors for gallbladder cancer: a polish case-control study. Int J Cancer. 1992;51(5):707–11.
12. Friedman GD. Natural history of asymptomatic and symptomatic gallstones. Am J Surg. 1993;165(4):399–404.
13. Schnelldorfer T. Porcelain gallbladder: a benign process or concern for malignancy? J Gastrointest Surg. 2013;17(6):1161–8.
14. Okamoto M, Okamoto H, Kitahara F, Kobayashi K, Karikome K, Miura K, et al. Ultrasonographic evidence of association of polyps and stones with gallbladder cancer. Am J Gastroenterol. 1999;94(2):446–50.
15. Aloia TA, Jarufe N, Javle M, Maithel SK, Roa JC, Adsay V, et al. Gallbladder cancer: expert consensus statement. HPB. 2015;17(8):681–90.
16. Voyles CR, Smadja C, Shands WC, Blumgart LH. Carcinoma in choledochal cysts. Age-related incidence. Arch Surg. 1983;118(8):986–8.
17. Elnemr A, Ohta T, Kayahara M, Kitagawa H, Yoshimoto K, Tani T, et al. Anomalous pancreaticobiliary ductal junction without bile duct dilatation in gallbladder cancer. Hepato-Gastroenterology. 2001;48(38):382–6.
18. Sogaard KK, Erichsen R, Lund JL, Farkas DK, Sorensen HT. Cholangitis and subsequent gastrointestinal cancer risk: a Danish population-based cohort study. Gut. 2014;63(2):356–61.
19. Nagaraja V, Eslick GD. Systematic review with meta-analysis: the relationship between chronic salmonella typhi carrier status and gall-bladder cancer. Aliment Pharmacol Ther. 2014;39(8):745–50.
20. Said K, Glaumann H, Bergquist A. Gallbladder disease in patients with primary sclerosing cholangitis. J Hepatol. 2008;48(4):598–605.
21. Kobayashi T, Harada K, Miwa K, Nakanuma Y. Helicobacter genus DNA fragments are commonly detectable in bile from patients with extrahepatic biliary diseases and associated with their pathogenesis. Dig Dis Sci. 2005;50(5):862–7.
22. Rai R, Sharma KL, Misra S, Kumar A, Mittal B. Cyp17 polymorphism (rs743572) is associated with increased risk of gallbladder cancer in tobacco users. Tumour Biol. 2014;35(7):6531–7.
23. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk:

a comprehensive dose-response meta-analysis. Br J Cancer. 2015;112(3):580–93.
24. Shebl FM, Andreotti G, Meyer TE, Gao YT, Rashid A, Yu K, et al. Metabolic syndrome and insulin resistance in relation to biliary tract cancer and stone risks: a population-based study in Shanghai, China. Br J Cancer. 2011;105(9):1424–9.
25. Yun SP, Shin N, Seo HI. Clinical outcomes of small cell neuroendocrine carcinoma and adenocarcinoma of the gallbladder. World J Gastroenterol. 2015;21(1):269–75.
26. Barreto SG, Dutt A, Chaudhary A. A genetic model for gallbladder carcinogenesis and its dissemination. Ann Oncol. 2014;25(6):1086–97.
27. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759–67.
28. Marks EI, Yee NS. Molecular genetics and targeted therapeutics in biliary tract carcinoma. World J Gastroenterol. 2016;22(4):1335–47.
29. Legan M, Luzar B, Marolt VF, Cor A. Expression of cyclooxygenase-2 is associated with p53 accumulation in premalignant and malignant gallbladder lesions. World J Gastroenterol. 2006;12(21):3425–9.
30. Wistuba II, Albores-Saavedra J. Genetic abnormalities involved in the pathogenesis of gallbladder carcinoma. J Hepato-Biliary-Pancreat Surg. 1999;6(3):237–44.
31. Legan M, Luzar B, Ferlan-Marolt V, Cor A. Cyclooxygenase-2 expression determines neo-angiogenesis in gallbladder carcinomas. Bosn J Basic Med Sci. 2006;6(4):58–63.
32. Wistuba II, Maitra A, Carrasco R, Tang M, Troncoso P, Minna JD, et al. High resolution chromosome 3p, 8p, 9q and 22q allelotyping analysis in the pathogenesis of gallbladder carcinoma. Br J Cancer. 2002;87(4):432–40.
33. Yoshida H, Shimada K, Kosuge T, Hiraoka N. A significant subgroup of resectable gallbladder cancer patients has an her2 positive status. Virchows Arch. 2016;468(4):431–9.
34. Chang HJ, Kim SW, Kim YT, Kim WH. Loss of heterozygosity in dysplasia and carcinoma of the gallbladder. Mod Pathol. 1999;12(8):763–9.
35. Wistuba II, Ashfaq R, Maitra A, Alvarez H, Riquelme E, Gazdar AF. Fragile histidine triad gene abnormalities in the pathogenesis of gallbladder carcinoma. Am J Pathol. 2002;160(6):2073–9.
36. Watanabe H, Date K, Itoi T, Matsubayashi H, Yokoyama N, Yamano M, et al. Histological and genetic changes in malignant transformation of gallbladder adenoma. Ann Oncol. 1999;10(Suppl 4):136–9.
37. Zhai G, Yan K, Ji X, Xu W, Yang J, Xiong F, et al. Laptm4b allele ∗2 is a marker of poor prognosis for gallbladder carcinoma. PLoS One. 2012;7(9):e45290.
38. Yuan LW, Liu DC, Yang ZL. Correlation of s1p1 and erp29 expression to progression, metastasis, and poor prognosis of gallbladder adenocarcinoma. Hepatobiliary Pancreat Dis Int. 2013;12(2):189–95.
39. Ghosh M, Sakhuja P, Singh S, Agarwal AK. P53 and beta-catenin expression in gallbladder tissues and correlation with tumor progression in gallbladder cancer. Saudi J Gastroenterol. 2013;19(1):34–9.
40. Wang YF, Feng FL, Zhao XH, Ye ZX, Zeng HP, Li Z, et al. Combined detection tumor markers for diagnosis and prognosis of gallbladder cancer. World J Gastroenterol. 2014;20(14):4085–92.
41. Huang HL, Yao HS, Wang Y, Wang WJ, Hu ZQ, Jin KZ. Proteomic identification of tumor biomarkers associated with primary gallbladder cancer. World J Gastroenterol. 2014;20(18):5511–8.
42. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, et al. Microrna expression profiles classify human cancers. Nature. 2005;435(7043):834–8.
43. Jin K, Xiang Y, Tang J, Wu G, Li J, Xiao H, et al. Mir-34 is associated with poor prognosis of patients with gallbladder cancer through regulating telomere length in tumor stem cells. Tumour Biol. 2014;35(2):1503–10.
44. Ma MZ, Chu BF, Zhang Y, Weng MZ, Qin YY, Gong W, et al. Long non-coding rna ccat1 promotes gallbladder cancer development via negative modulation of mirna-218-5p. Cell Death Dis. 2015;6:e1583.
45. Peng HH, Zhang YD, Gong LS, Liu WD, Zhang Y. Increased expression of microrna-335 predicts a favorable prognosis in primary gallbladder carcinoma. Onco Targets Ther. 2013;6:1625–30.
46. Kitamura T, Connolly K, Ruffino L, Ajiki T, Lueckgen A, DiGiovanni J, et al. The therapeutic effect of histone deacetylase inhibitor pci-24781 on gallbladder carcinoma in bk5.Erbb2 mice. J Hepatol. 2012;57(1):84–91.
47. Chang Y, Liu C, Yang J, Liu G, Feng F, Tang J, et al. Mir-20a triggers metastasis of gallbladder carcinoma. J Hepatol. 2013;59(3):518–27.
48. Kono H, Nakamura M, Ohtsuka T, Nagayoshi Y, Mori Y, Takahata S, et al. High expression of microrna-155 is associated with the aggressive malignant behavior of gallbladder carcinoma. Oncol Rep. 2013;30(1):17–24.
49. Qiu Y, Luo X, Kan T, Zhang Y, Yu W, Wei Y, et al. Tgf-beta upregulates mir-182 expression to promote gallbladder cancer metastasis by targeting cadm1. Mol BioSyst. 2014;10(3):679–85.
50. Glazer ES, Liu P, Abdalla EK, Vauthey JN, Curley SA. Neither neoadjuvant nor adjuvant therapy increases survival after biliary tract cancer resection with wide negative margins. J Gastrointest Surg. 2012;16(9):1666–71.
51. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase iii multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer. 2002;95(8):1685–95.
52. Wang SJ, Lemieux A, Kalpathy-Cramer J, Ord CB, Walker GV, Fuller CD, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29(35):4627–32.
53. Konishi M. Adjuvant chemotherapy for resectable biliary tract cancer: current status and future direction. Journal of Hepatobiliary Pancreat Sci. 2012;19(4):301–5.
54. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(16):1934–40.
55. Ben-Josef E, Guthrie KA, El-Khoueiry AB, Corless CL, Zalupski MM, Lowy AM, et al. Swog s0809: a phase ii intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(24):2617–22.
56. Benson AB 3rd, D'Angelica MI, Abbott D, Abrams TA, Alberts SR, Saenz DA, Are C, Brown D, Chang DT, Covey AM, Hawkins W, Iyer R, Jacob R, Karachristos A, Kelley RK, Kim R, Palta M, Park JO, Sahai V, Schefter T, Schmidt C, Sicklick JK, Singh G, Sohal D, Stein S, Tian GG, Vauthey J, Venook AP, Zhu AX. Hepatobiliary cancers, version 1.2017, NCCN clinical practice guidelines in oncology. Available through https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. 2017.
57. Dingle BH, Rumble RB, Brouwers MC. Cancer Care Ontario's Program in Evidence-Based Care's Gastrointestinal Cancer Disease Site G. The role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer: a systematic review. Can J Gastroenterol. 2005;19(12):711–6.
58. Knox JJ, Hedley D, Oza A, Feld R, Siu LL, Chen E, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase ii trial. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(10):2332–8.

59. Riechelmann RP, Townsley CA, Chin SN, Pond GR, Knox JJ. Expanded phase ii trial of gemcitabine and capecitabine for advanced biliary cancer. Cancer. 2007;110(6):1307–12.
60. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer. 2007;96(6):896–902.
61. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81.
62. Sharma A, Dwary AD, Mohanti BK, Deo SV, Pal S, Sreenivas V, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(30):4581–6.
63. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, et al. Genomic spectra of biliary tract cancer. Nat Genet. 2015;47(9):1003–10.
64. Borger DR, Tanabe KK, Fan KC, Lopez HU, Fantin VR, Straley KS, et al. Frequent mutation of isocitrate dehydrogenase (idh)1 and idh2 in cholangiocarcinoma identified through broad-based tumor genotyping. Oncologist. 2012;17(1):72–9.
65. Kipp BR, Voss JS, Kerr SE, Barr Fritcher EG, Graham RP, Zhang L, et al. Isocitrate dehydrogenase 1 and 2 mutations in cholangiocarcinoma. Hum Pathol. 2012;43(10):1552–8.
66. Farshidfar F, Zheng S, Gingras MC, Newton Y, Shih J, Robertson AG, et al. Integrative genomic analysis of cholangiocarcinoma identifies distinct idh-mutant molecular profiles. Cell Rep. 2017;18(11):2780–94.
67. Churi CR, Shroff R, Wang Y, Rashid A, Kang HC, Weatherly J, et al. Mutation profiling in cholangiocarcinoma: Prognostic and therapeutic implications. PLoS One. 2014;9(12):e115383.
68. Baselga J. Why the epidermal growth factor receptor? The rationale for cancer therapy. Oncologist. 2002;7(Suppl 4):2–8.
69. Chang YT, Chang MC, Huang KW, Tung CC, Hsu C, Wong JM. Clinicopathological and prognostic significances of egfr, kras and braf mutations in biliary tract carcinomas in taiwan. J Gastroenterol Hepatol. 2014;29(5):1119–25.
70. Philip PA, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, et al. Phase ii study of erlotinib in patients with advanced biliary cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(19):3069–74.
71. Lee J, Park SH, Chang HM, Kim JS, Choi HJ, Lee MA, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. The Lancet Oncology. 2012;13(2):181–8.
72. Riley E, Carloss H. Dramatic response to panitumumab and bevacizumab in metastatic gallbladder carcinoma. Oncologist. 2011;16(5):e1–2.
73. Gruenberger B, Schueller J, Heubrandtner U, Wrba F, Tamandl D, Kaczirek K, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. Lancet Oncol. 2010;11(12):1142–8.
74. Malka D, Cervera P, Foulon S, Trarbach T, de la Fouchardiere C, Boucher E, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (bingo): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol. 2014;15(8):819–28.
75. Hezel AF, Noel MS, Allen JN, Abrams TA, Yurgelun M, Faris JE, et al. Phase ii study of gemcitabine, oxaliplatin in combination with panitumumab in kras wild-type unresectable or metastatic biliary tract and gallbladder cancer. Br J Cancer. 2014;111(3):430–6.
76. Leone F, Marino D, Cereda S, Filippi R, Belli C, Spadi R, et al. Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in wild-type kras advanced biliary tract cancer: a randomized phase 2 trial (vecti-bil study). Cancer. 2016;122(4):574–81.
77. Zaczek A, Brandt B, Bielawski KP. The diverse signaling network of egfr, her2, her3 and her4 tyrosine kinase receptors and the consequences for therapeutic approaches. Histol Histopathol. 2005;20(3):1005–15.
78. Nakazawa K, Dobashi Y, Suzuki S, Fujii H, Takeda Y, Ooi A. Amplification and overexpression of c-erbb-2, epidermal growth factor receptor, and c-met in biliary tract cancers. J Pathol. 2005;206(3):356–65.
79. Papadopoulou E, Metaxa-Mariatou V, Tsaousis G, Tsoulos N, Tsirigoti A, Efstathiadou C, et al. Molecular predictive markers in tumors of the gastrointestinal tract. World J Gastrointest Oncol. 2016;8(11):772–85.
80. Yoshikawa D, Ojima H, Iwasaki M, Hiraoka N, Kosuge T, Kasai S, et al. Clinicopathological and prognostic significance of egfr, vegf, and her2 expression in cholangiocarcinoma. Br J Cancer. 2008;98(2):418–25.
81. Ramanathan RK, Belani CP, Singh DA, Tanaka M, Lenz HJ, Yen Y, et al. A phase ii study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. Cancer Chemother Pharmacol. 2009;64(4):777–83.
82. Javle M, Churi C, Kang HC, Shroff R, Janku F, Surapaneni R, et al. Her2/neu-directed therapy for biliary tract cancer. J Hematol Oncol. 2015;8:58.
83. Peck J, Wei L, Zalupski M, O'Neil B, Villalona Calero M, Bekaii-Saab T. Her2/neu may not be an interesting target in biliary cancers: results of an early phase ii study with lapatinib. Oncology. 2012;82(3):175–9.
84. McMahon G. Vegf receptor signaling in tumor angiogenesis. Oncologist. 2000;5(Suppl 1):3–10.
85. Nakashima T, Kondoh S, Kitoh H, Ozawa H, Okita S, Harada T, et al. Vascular endothelial growth factor-c expression in human gallbladder cancer and its relationship to lymph node metastasis. Int J Mol Med. 2003;11(1):33–9.
86. Zhu AX, Meyerhardt JA, Blaszkowsky LS, Kambadakone AR, Muzikansky A, Zheng H, et al. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose pet with clinical outcome: a phase 2 study. Lancet Oncol. 2010;11(1):48–54.
87. Iyer RV, Pokuri VK, Groman A, Ma WW, Malhotra U, Iancu DM, et al. A multicenter phase ii study of gemcitabine, capecitabine, and bevacizumab for locally advanced or metastatic biliary tract cancer. Am J Clin Oncol. 2018;41(7):649–55.
88. Lubner SJ, Mahoney MR, Kolesar JL, Loconte NK, Kim GP, Pitot HC, et al. Report of a multicenter phase ii trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase ii consortium study. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(21):3491–7.
89. Bengala C, Bertolini F, Malavasi N, Boni C, Aitini E, Dealis C, et al. Sorafenib in patients with advanced biliary tract carcinoma: a phase ii trial. Br J Cancer. 2010;102(1):68–72.
90. Lee JK, Capanu M, O'Reilly EM, Ma J, Chou JF, Shia J, et al. A phase ii study of gemcitabine and cisplatin plus sorafenib in patients with advanced biliary adenocarcinomas. Br J Cancer. 2013;109(4):915–9.
91. LoConte NK, Holen KD, Schelman WR, Mulkerin DL, Deming DA, Hernan HR, et al. A phase i study of sorafenib, oxaliplatin and 2 days of high dose capecitabine in advanced pancreatic and biliary tract cancer: a wisconsin oncology network study. Investig New Drugs. 2013;31(4):943–8.
92. Maulik G, Shrikhande A, Kijima T, Ma PC, Morrison PT, Salgia R. Role of the hepatocyte growth factor receptor, c-met, in oncogenesis and potential for therapeutic inhibition. Cytokine Growth Factor Rev. 2002;13(1):41–59.
93. Yang L, Guo T, Jiang S, Yang Z. Expression of ezrin, hgf and c-met and its clinicopathological significance in the benign and

malignant lesions of the gallbladder. Hepato-Gastroenterology. 2012;59(118):1769–75.
94. Presta M, Dell'Era P, Mitola S, Moroni E, Ronca R, Rusnati M. Fibroblast growth factor/fibroblast growth factor receptor system in angiogenesis. Cytokine Growth Factor Rev. 2005;16(2):159–78.
95. Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. Oncologist. 2014;19(3):235–42.
96. Pharmaceuticals N. A phase ii, single arm study of bgj398 in patients with advanced cholangiocarcinoma. Available through https://clinicaltrials.gov/ct2/show/NCT02150967?term=NCT02150967&rank=1.
97. McCubrey JA, Steelman LS, Chappell WH, Abrams SL, Wong EW, Chang F, et al. Roles of the raf/mek/erk pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta. 2007;1773(8):1263–84.
98. Bekaii-Saab T, Phelps MA, Li X, Saji M, Goff L, Kauh JS, et al. Multi-institutional phase ii study of selumetinib in patients with metastatic biliary cancers. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29(17):2357–63.
99. Bridgewater J, Lopes A, Beare S, Duggan M, Lee D, Ricamara M, et al. A phase 1b study of selumetinib in combination with cisplatin and gemcitabine in advanced or metastatic biliary tract cancer: the abc-04 study. BMC Cancer. 2016;16:153.
100. Cardone MH, Roy N, Stennicke HR, Salvesen GS, Franke TF, Stanbridge E, et al. Regulation of cell death protease caspase-9 by phosphorylation. Science (New York, NY). 1998;282(5392):1318–21.
101. Hansel DE, Rahman A, Hidalgo M, Thuluvath PJ, Lillemoe KD, Schulick R, et al. Identification of novel cellular targets in biliary tract cancers using global gene expression technology. Am J Pathol. 2003;163(1):217–29.
102. Thant AA, Nawa A, Kikkawa F, Ichigotani Y, Zhang Y, Sein TT, et al. Fibronectin activates matrix metalloproteinase-9 secretion via the mek1-mapk and the pi3k-akt pathways in ovarian cancer cells. Clin Exp Metastasis. 2000;18(5):423–8.
103. Zoncu R, Efeyan A, Sabatini DM. Mtor: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol. 2011;12(1):21–35.
104. Herberger B, Puhalla H, Lehnert M, Wrba F, Novak S, Brandstetter A, et al. Activated mammalian target of rapamycin is an adverse prognostic factor in patients with biliary tract adenocarcinoma. Clin Cancer Res. 2007;13(16):4795–9.
105. Costello BA, Borad MJ, Qi Y, Kim GP, Northfelt DW, Erlichman C, et al. Phase i trial of everolimus, gemcitabine and cisplatin in patients with solid tumors. Investig New Drugs. 2014;32(4):710–6.
106. Li Q, Mou LJ, Tao L, Chen W, Sun XT, Xia XF, et al. Inhibition of mtor suppresses human gallbladder carcinoma cell proliferation and enhances the cytotoxicity of 5-fluorouracil by downregulating mdr1 expression. Eur Rev Med Pharmacol Sci. 2016;20(9):1699–706.
107. Mohri D, Ijichi H, Miyabayashi K, Takahashi R, Kudo Y, Sasaki T, et al. A potent therapeutics for gallbladder cancer by combinatorial inhibition of the mapk and mtor signaling networks. J Gastroenterol. 2016;51(7):711–21.

Hepatocellular Carcinoma

13

Sahin Lacin, Asif Rashid, Yun Shin Chun, Bruno Calazans Odisio, Eugene J. Koay, Reham Abdel-Wahab, and Ahmed O. Kaseb

Hepatocellular Carcinoma

Introduction

Worldwide, hepatocellular carcinoma (HCC) is the sixth most common cancer and the second most common cause of cancer mortality. Also, it is the fifth most common cancer in men (554,000 cases/year, 7.5% of all cases) and the ninth most common cancer in women (228,000 cases/year, 3.4% of all cases). Globally, liver cancer develops in an estimated 782,000 people each year, and 745,000 die of it annually [1].

Many factors increase the risk of HCC. These risk factors are classified into two groups: preventable and non-preventable. Preventable risk factors are hepatitis B and C virus (HBV and HCV) infections, obesity, diabetes, nonalcoholic steatohepatitis, toxic exposures (e.g., aflatoxins, vinyl chloride), and alcohol, tobacco, and drug use [2–4]. Non-preventable risk factors are race or ethnicity, age, sex, family history, hereditary hemochromatosis, α(alpha)-1 antitrypsin deficiency, autoimmune hepatitis, and subtypes of porphyria [4–7]. Worldwide, the most frequent underlying cause of HCC is chronic hepatitis B virus infection, whereas in developed countries, such as those in Southern Europe and North America, the most common cause is chronic hepatitis C infection. The vast majority of patients with HCC have cirrhosis, although HCC may develop in patients with chronic hepatitis B virus infection without evidence of cirrhosis [8, 9]. HCC is usually detected earlier in cirrhotic patients than in those with normal livers owing to regular screening in follow-up examinations. However, HCCs remain asymptomatic for longer periods and often present with large tumor diameters at the time of diagnosis in patients with normal livers [10, 11].

Histopathology of Hepatocellular Carcinoma

Gross Findings

An HCC usually presents as a nodular mass rimmed with a pseudocapsule (most often in a cirrhotic liver) or encapsulated (most often in a noncirrhotic liver) [12, 13]. The tumor is often soft, with or without areas of necrosis, and yellow, tan, grayish-white, or green (owing to bile production) in color. Invasion into the portal and hepatic veins and vena cava is common, but invasion into bile ducts is uncommon. An HCC can be either a single nodule with or without adjacent satellite nodules or multifocal owing to multicentric (multiclonal) tumors or intrahepatic metastasis from a primary site. It can also present as a massive dominant mass with or without satellite nodules; a pedunculated tumor protruding from the liver with or without a pedicle; or a diffuse tumor with numerous small nodules diffusely infiltrating the liver parenchyma. The lungs, lymph nodes, bone, and adrenal glands are the most common sites of extrahepatic metastasis of HCC.

S. Lacin
Department of Medical Oncology, Hacettepe Üniversitesi Sıhhiye Yerleşkesi, Altındağ, Ankara, Turkey

A. Rashid
Department of Pathology, Division of Pathology/Lab Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Y. S. Chun (✉)
Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: yschun@mdanderson.org

B. C. Odisio
Department of Interventional Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

E. J. Koay
Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

R. Abdel-Wahab
Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

A. O. Kaseb
Department of GI Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_13

Light Microscopic Findings

Diagnosis of HCC requires demonstration of hepatocellular differentiation by tumor cells and features of malignancy [12, 13]. These can be demonstrated by light microscopy, special stains, or immunohistochemical or ultrastructural studies. The spectrum of histologic findings for HCC varies from resembling normal liver parenchyma to anaplastic tumors with little hepatocellular differentiation. Most HCCs have definitive hepatocellular differentiation in a trabecular pattern in sinusoid-like blood spaces but characteristically lack portal tracts (Fig. 13.1), a feature shared by hepatic adenomas. The tumor cells are moderately sized and polygonal; have eosinophilic, finely granular cytoplasm and distinct cell membranes; grow in hepatic plates at least 3 cells thick; and have a bile canaliculus running through the plate and a single layer of endothelial cells lining both sides of the plate. The normal reticulin network of liver parenchyma is reduced and disrupted, and reticulin staining is employed to distinguish HCCs from nonneoplastic liver parenchyma and hepatic adenomas. Another common histologic variant is a pseudoglandular or pseudoacinar pattern formed by abnormal or dilated bile canaliculi (Fig. 13.2). Bile plugs in dilated bile canaliculi or pseudoglands can help establish the diagnosis of HCC. A solid or compact pattern of HCC has sheets of tumor cells with compressed trabeculae and sinusoids (Fig. 13.3). The clear-cell variant of HCC can have fat vacuoles or glycogen in the cytoplasm and clear cytoplasm (Fig. 13.4). This variant must be differentiated from metastatic clear-cell renal cell carcinoma.

A variety of intracytoplasmic inclusions can be present in HCCs [12, 13]. Mallory-Denk bodies, which are similar to Mallory bodies, are irregular, eosinophilic, periodic acid-Schiff–negative aggregated intermediate filaments, such as

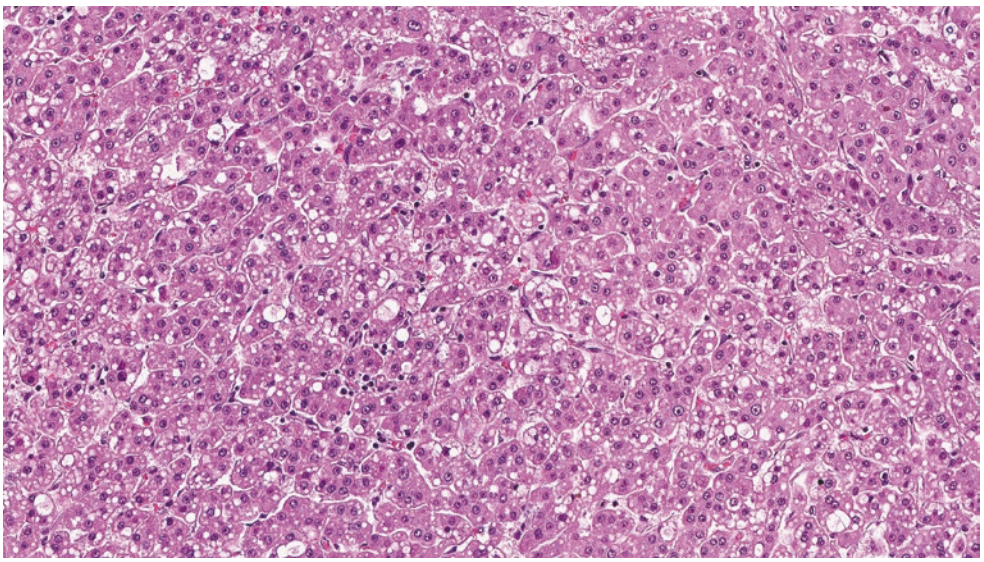


Fig. 13.1 Moderately differentiated hepatocellular carcinoma with a trabecular pattern, increased thickness of hepatic plates separated by sinusoids (400× magnification, H&E stain)

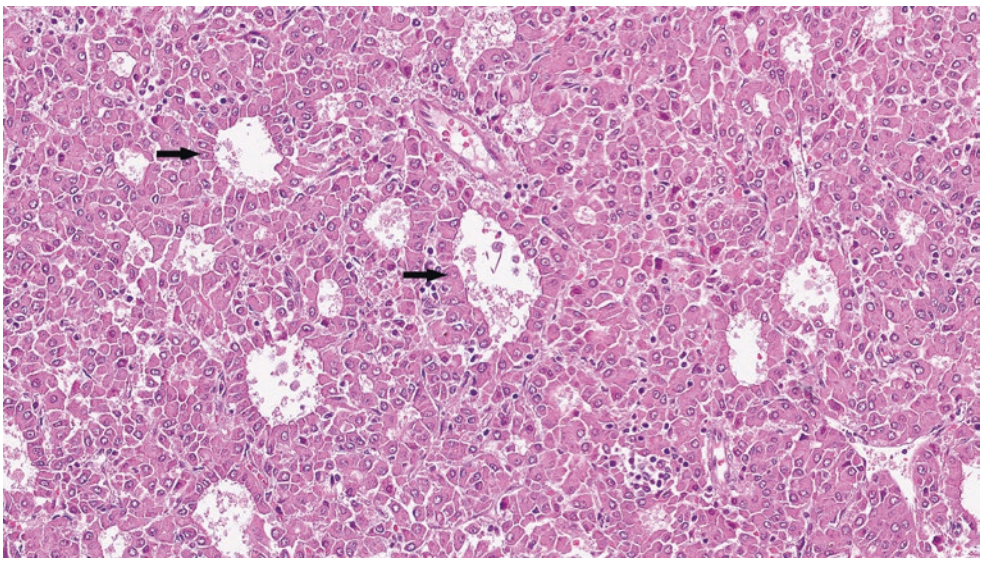


Fig. 13.2 Moderately differentiated hepatocellular carcinoma with a pseudoglandular pattern designated by arrows (400× magnification, H&E stain)

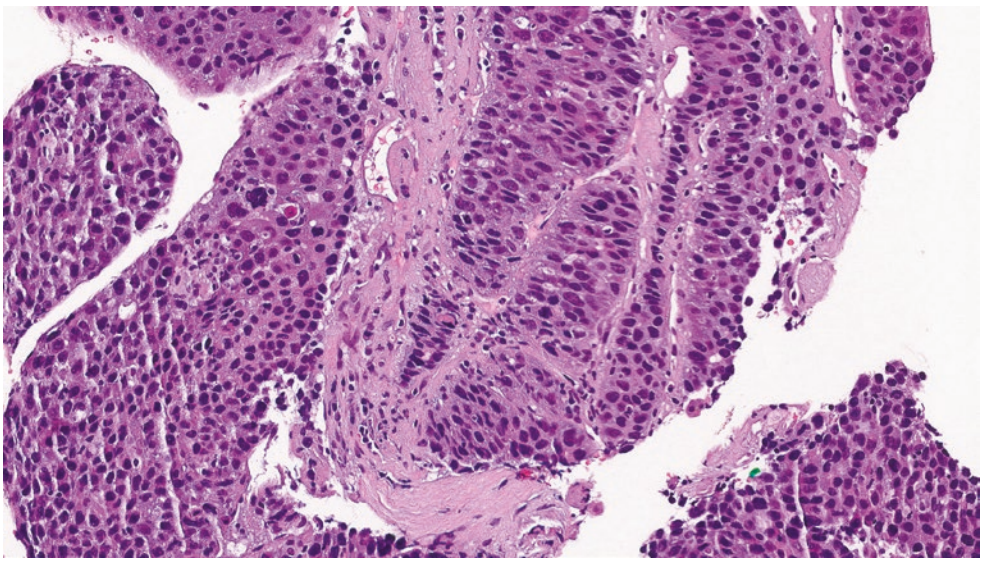


Fig. 13.3 Poorly differentiated hepatocellular carcinoma with a solid pattern (400× magnification, H&E stain)

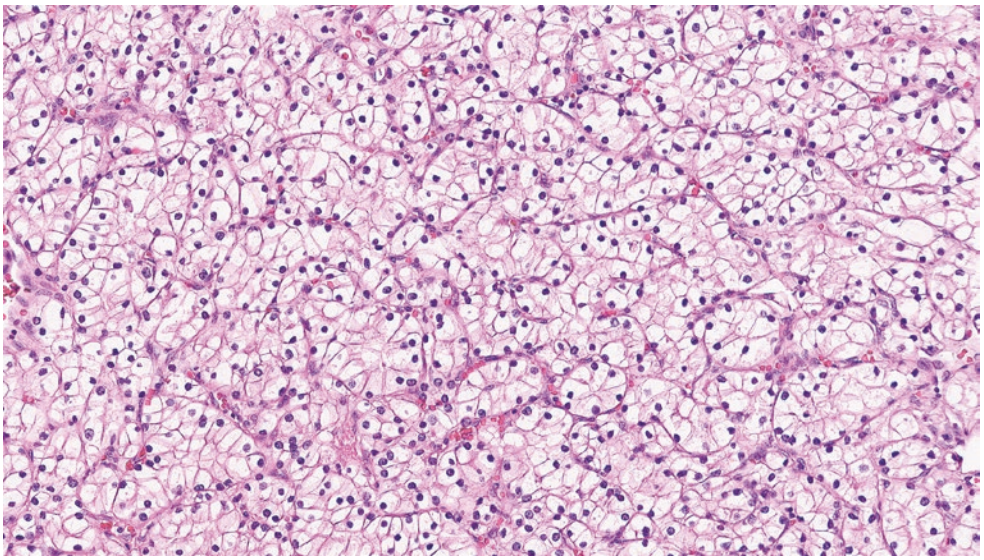


Fig. 13.4 Moderately differentiated hepatocellular carcinoma clear-cell type with clear cytoplasm (400× magnification, H&E stain)

ubiquitin and keratins. Hyaline bodies, which are similar to globules that accumulate in patients who have α(alpha)-1-antitrypsin deficiency, are globular, round, strongly eosinophilic, periodic acid-Schiff-positive, and diastase-resistant owing to α(alpha)-1-antitrypsin accumulation (Fig. 13.5). Pale bodies are round-to-oval, amorphous, and lightly eosinophilic owing to accumulated fibrinogen in the endoplasmic reticulum. Rarely, ground-glass inclusions, similar to those in HBsAg-positive hepatocytes, can be present in neoplastic cells in HCCs arising in HBsAg-positive patients. Except for ground-glass inclusions, which can be present in patients with hepatitis B virus infection, other inclusions are not specific to the underlying liver disease.

Other uncommon variants of HCC include scirrhous carcinoma with marked fibrosis along the sinusoid-like spaces, undifferentiated carcinoma with hepatocellular differentiation demonstrated using immunohistochemistry but that cannot be classified further, lymphoepithelioma-like carcinoma with numerous intratumoral lymphocytes, and sarcomatoid carcinoma with malignant spindle cells.

Fibrolamellar Hepatocellular Carcinoma

Fibrolamellar HCC is a rare distinctive type of this tumor that is most common in children and young adults [12, 13]. Grossly, the tumor is yellow to pale tan and firm and may have a central scar. Histologically, the tumor is composed of large polygonal cells with abundant eosinophilic cytoplasm, large vesicular nuclei, large distinct nucleoli, and tumor nests surrounded by characteristic lamellar fibrosis (Fig. 13.6). These tumors can have glandular differentiation with mucin production. Pale bodies, hyaline bodies, and calcification may be present in fibrolamellar HCCs.

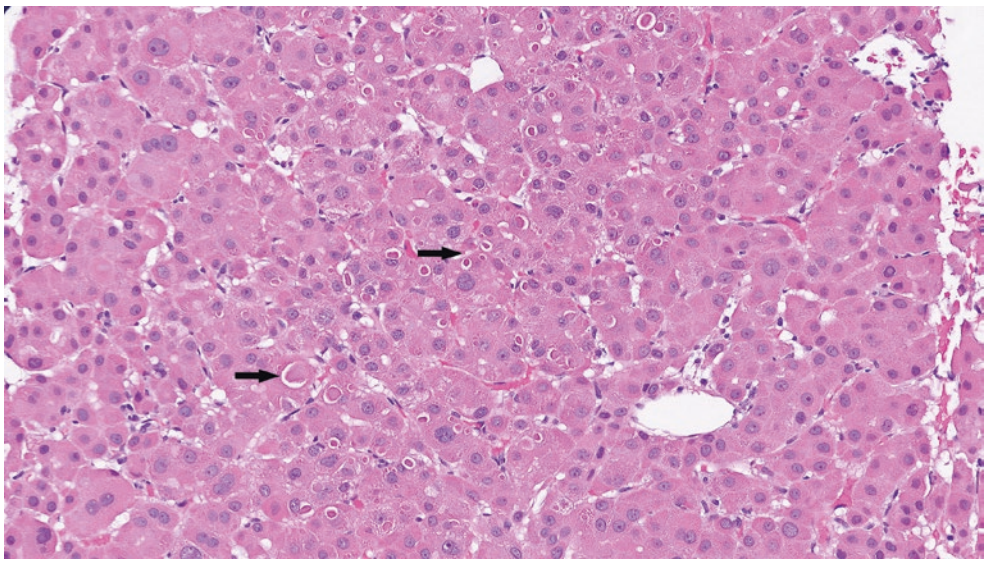


Fig. 13.5 Hepatocellular carcinoma with hyaline globules designated by arrows (400× magnification, H&E stain)

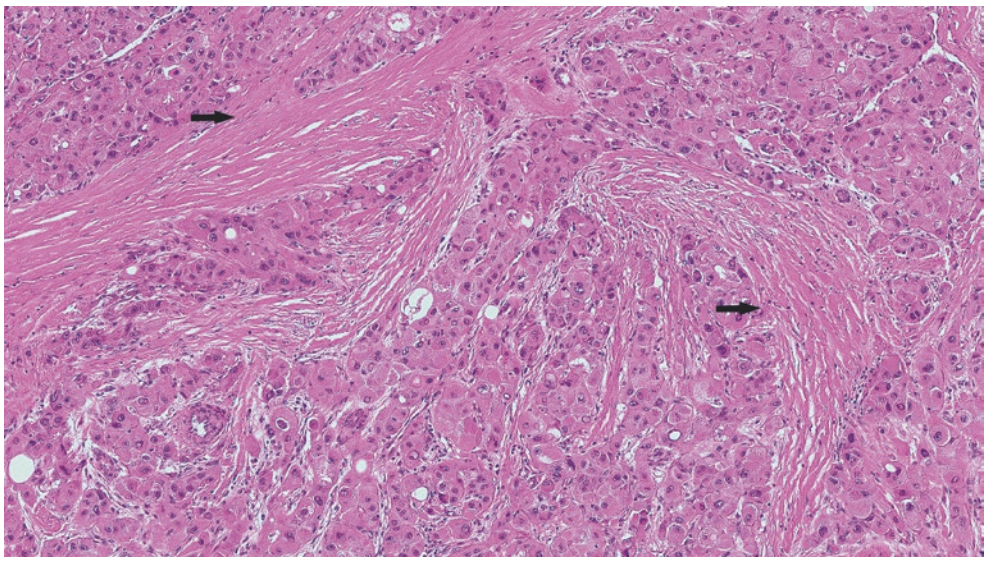


Fig. 13.6 Fibrolamellar hepatocellular carcinoma with large, eosinophilic cells, and lamellar fibrosis designated by arrows (200× magnification, H&E stain)

Immunohistochemical Findings

Immunohistochemistry can be used to confirm hepatocellular differentiation and distinguish HCC from benign liver lesions and other primary and metastatic liver tumors [12, 13]. HepPar-1 and arginase are sensitive markers of hepatocellular differentiation, although the former is occasionally present in stomach cancers and cholangiocarcinomas. Glypican-3 can be used to distinguish HCC from hepatic adenoma and benign liver lesions [14]. The bile canaliculi in HCCs can be demonstrated by immunohistochemistry for polyclonal carcinoembryonic antigen and CD10. In contrast with normal sinusoids, the sinusoidal-like spaces in HCCs exhibit changes in "capillarization" and stain for CD34. In contrast to HCC, carcinoembryonic antigen has cytoplasmic staining in adenocarcinomas. HCCs stain for cytokeratin 8 and 18 recognized by CAM 5.2 but do not stain for high-molecular-weight cytokeratins recognized by AE1/AE3 or biliary-type cytokeratins 7 and 19. Most HCCs do not stain for antibodies against cytokeratin 7 or cytokeratin 20, but they occasionally can be positive for them, especially cytokeratin 7. HCCs do not stain for epithelial membrane antigen or MOC31. Serum α(alpha)-fetoprotein levels are high in most HCC patients, but very few HCCs are stainable for α(alpha)-fetoprotein. In situ hybridization for albumin can be invaluable in demonstrating hepatocellular differentiation in difficult HCC cases [15].

Differential Diagnosis

HCCs must be distinguished from primary liver lesions and a wide variety of metastatic tumors [12, 13]. One of the most difficult problems in liver pathology is distinguishing a well-differentiated HCC from a hepatic adenoma. This can be a

problem even with a resected tumor. Reticulin staining to demonstrate increased trabecular thickness and loss of reticulin architecture and a lack of use of oral contraceptives or androgens can help to differentiate HCCs from hepatic adenomas in a few cases. Some studies have performed chromosomal analyses and nuclear staining for β(beta)-catenin immunohistochemistry in hepatic adenomas to help in difficult and problematic cases [16]. Macroregenerative nodules in patients with cirrhosis may have some cytologic atypia or abnormal trabecular growth patterns. Preservation of normal hepatic architecture by reticulin stain and lack of staining for glypican-3 immunohistochemistry can be invaluable in differentiating macroregenerative nodules from HCCs. Focal nodular hyperplasia can mimic fibrolamellar HCC in imaging studies and grossly with a central scar, but it has a distinct histology.

HCCs have large eosinophilic cells and can mimic other tumors with similar histologies, including neuroendocrine tumors and carcinomas, adrenocortical carcinomas, mesotheliomas, melanomas, gastrointestinal stromal tumors, and angiomyolipomas. Well-intermediate-grade pancreatic gastrointestinal neuroendocrine tumors and carcinomas can histologically mimic HCCs; this is one of the most common misdiagnoses in liver neoplastic pathology. Elevated serum neuropeptide levels, imaging studies, and immunohistochemistry for chromogranin and synaptophysin can help with this differential diagnosis. Similarly, adrenocortical carcinoma can be easily distinguished from HCC via immunohistochemistry for inhibin, calretinin, and melan-A. Although most clear-cell variants of HCC can have conventional trabecular patterns with eosinophilic cells, metastatic clear-cell renal cell carcinoma should be excluded by immunohistochemistry positive for epithelial membrane antigen, CD10, and PAX88 and negative for pan-cytokeratin.

A primary cholangiocarcinoma or metastatic adenocarcinoma can be difficult to differentiate from a poorly differentiated HCC [17]. Immunohistochemistry for hepatic markers, including HepPar-1, arginase, polyclonal carcinoembryonic antigen, cytokeratins 7 and 20, and MOC31, and a variety of site-specific markers, such as napsin A, TTF-1, CDX-2, PAX8, WT-1, calretinin, estrogen receptor, and progesterone receptor, may help in differential diagnosis of HCC.

Grading of Hepatocellular Carcinomas

HCCs are graded as well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated [12, 13]. Well-differentiated carcinomas have mild cytologic atypia, increased nucleus-to-cytoplasmic ratios, thin trabeculae composed of 3 or fewer cells in thickness, and pseudoglandular patterns. Moderately differentiated HCCs have trabecular growth of 3 or more cells in thickness, their cells have abundant eosinophilic cytoplasm with round nuclei and distinct nucleoli, and they have pseudoglandular histologic pattern. Poorly differentiated carcinomas have a solid-tumor growth pattern without distinct sinusoid-like blood spaces, and their cells have increased nucleus-to-cytoplasm ratios and moderate to marked pleomorphism. Undifferentiated carcinomas have a solid growth pattern with round or spindle tumor cells containing little cytoplasm.

Staging of Hepatocellular Carcinomas

HCCs are staged using the American Joint Committee on Cancer tumor-node-metastasis (TNM) classification [18]. This classification uses the number and size of tumor nodules; presence or absence of vascular invasion, including that of major branches of the portal and hepatic veins; involvement of adjacent organs; involvement of the visceral peritoneum; and lymph node or distant metastasis (Table 13.1).

Table 13.1 Pathologic staging of hepatocellular carcinoma using the tumor-node-metastasis (TNM) system [18]

Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm or >2 cm without vascular invasion
T1a	Solitary tumor ≤ 2 cm
T1b	Solitary tumor > 2 cm without vascular invasion
T2	Solitary tumor > 2 cm with vascular invasion, or multiple tumors, none > 5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC prognostic stage groups			
When T is…	And N is…	And M is…	Then the stage group is…
T1a	N0	M0	IA
T1b	N0	M0	I B
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IVA
Any T	Any N	M1	IVB

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

Nonalcoholic Steatohepatitis-Related Hepatocellular Carcinoma

Nonalcoholic fatty liver disease is the most common cause of liver dysfunction, and its prevalence is 20–30% in the general population and up to 57–74% in obese individuals [19]. Nonalcoholic fatty liver disease increases the liver's susceptibility to oxidative stress and inflammatory cytokines such as interleukin-6 and tumor necrosis factor, with subsequent progression to nonalcoholic steatohepatitis and fibrosis. Recently, a large retrospective study demonstrated that the proportion of nonviral-related HCC in all HCC patients increased from 10.0% in 1991 to 24.1% in 2001, with most cases related to nonalcoholic fatty liver disease and diabetes [20].

Sex Hormone-Related Hepatocellular Carcinoma

As far as we know, irrespective of worldwide variation in incidence, HCC is a male-dominant disease. Particularly, in sub-Saharan Africa, the incidence of HCC in men is up to 10 times higher than that in women [21]. The liver expresses estrogen and androgen receptors, which may act as transcription factors and regulate the expression of several regulatory genes. These genes are involved in several pathways associated with cell proliferation and immune response [22, 23]. Both estrogen and androgen are steroid hormones that mediate their own action by binding to nuclear receptors and acting as transcription factors to regulate expression of multiple genes as described previously. Researchers have shown that progression from hyperplasia to HCC is associated with suppressed estrogen-receptor expression and elevated androgen-receptor expression [24–27].

Role of Surgery for Hepatocellular Carcinoma

Hepatic resection is the primary treatment of HCC in selected patients who do not meet criteria for liver transplantation or local ablation. Published 5-year overall survival (OS) rates after hepatic resection for HCC range from 25% to 80% depending on patient selection and pathologic factors [28–30]. However, a minority of patients with HCC are candidates for hepatic resection owing to advanced disease stage at diagnosis, underlying chronic liver disease, and/or hepatic dysfunction. In addition, hepatic resection is associated with high intrahepatic tumor recurrence rates of 50% at 3 years and 70% at 5 years. Important considerations before performing partial hepatectomy for HCC include assessment of hepatic reserve, the anticipated extent of the resection, and prognostic factors.

Assessment of Hepatic Reserve

The degree of fibrosis and hepatic dysfunction are critical factors in selecting patients with HCC for hepatic resection. The most widely used classification scheme for assessing the degree of cirrhosis is the Child-Pugh score. Components of the Child-Pugh classification are two clinical factors—encephalopathy and ascites—and three laboratory values—prothrombin time, albumin level, and bilirubin level. In general, patients with Child-Pugh A cirrhosis and highly selected patients with Child-Pugh B disease are candidates for hepatic resection. Another preoperative tool to select cirrhotic patients for hepatic resection is the Model for End-Stage Liver Disease (MELD) score, which is based on serum bilirubin and creatinine levels and the international normalized ratio (INR). A study at the Mayo Clinic demonstrated that a MELD score lower than 9 was associated with no perioperative mortality after resection of HCC in cirrhotic patients, whereas 29% of patients with a MELD score of 9 or higher died perioperatively ($p < 0.01$) [31]. The results of this study were validated in a report by Cucchetti and colleagues, in which the rate of postoperative liver failure in patients with a MELD score lower than 9 was 0% versus 38% in those with a MELD score greater than 10 ($p = 0.001$) [32].

An important preoperative consideration in patients with HCC is the presence of portal hypertension, reflected by thrombocytopenia, a hepatic venous gradient greater than 10 mm Hg, and the presence of esophageal varices, ascites, and/or splenomegaly. In patients with portal hypertension, morbidity and mortality rates are prohibitive after major hepatectomy, but selected patients may undergo resection of 1 or 2 segments safely. Ishizawa and coworkers compared outcomes after hepatic resection in patients with ($n = 136$) and without ($n = 250$) portal hypertension, defined as the presence of esophageal varices or a platelet count less than 100,000/mm in association with splenomegaly [33]. The extent of liver resection was limited to less than 1 sector in 98% of the patients with portal hypertension. Patients with portal hypertension had a postoperative complication rate of 10%, which was not significantly different from that in patients without portal hypertension (12%). The 5-year OS rate was significantly shorter in patients with portal hypertension: 56% versus 71% in those without it ($p = 0.008$). In a multivariate analysis, vascular invasion and Child-Pugh B score but not portal hypertension were independent predictors of OS.

Absolute contraindications for both major and minor hepatic resection are a bilirubin level greater than 2 mg/dL, the presence of ascites, and an insufficient liver remnant volume.

Liver Volumetry and Portal Vein Embolization

An insufficient anticipated volume of liver remaining after resection, or future liver remnant (FLR) volume, is a contra-

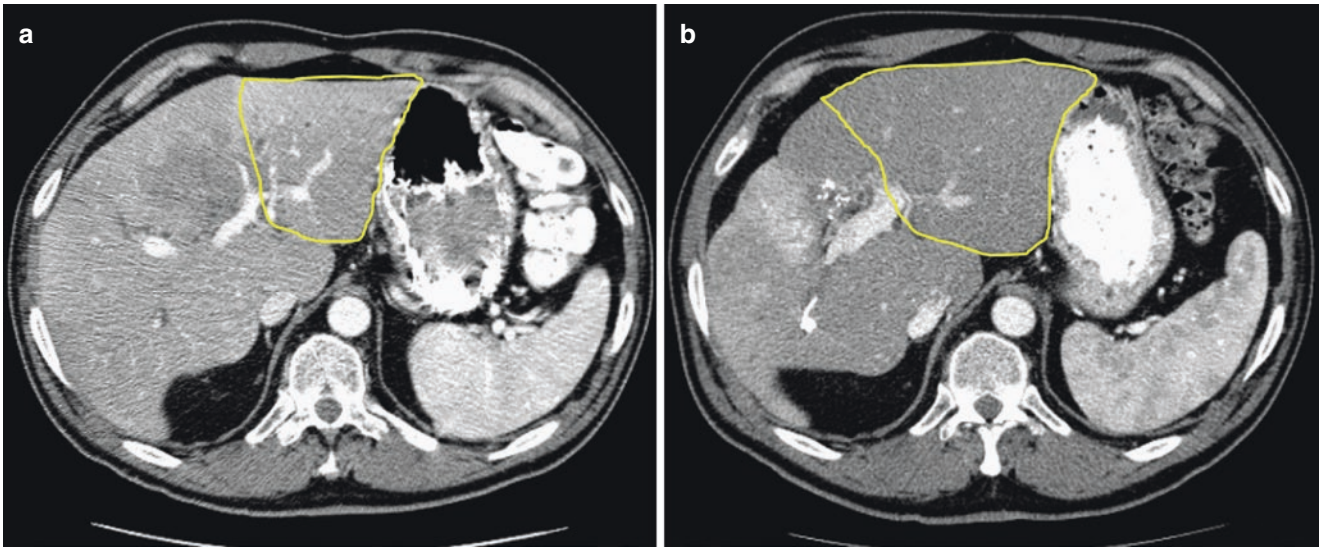


Fig. 13.7 Tumor necrosis and left liver hypertrophy before (**a**) and after (**b**) sequential TACE and PVE for HCC. The yellow line indicates the remnant liver volume

indication for hepatic resection. In patients without underlying chronic liver disease, the recommended FLR volume is 20%. However, in cirrhotic patients who have impaired hepatic reserve and diminished regenerative capacity, the recommended FLR volume is 40% [34]. In patients whose FLR volume is insufficient, portal vein embolization (PVE) is a strategy for enabling safe hepatectomy. PVE is performed by an interventional radiologist and involves embolization of the portal vein tree supplying the side of the liver to be resected, usually the right liver. PVE induces atrophy of the ipsilateral embolized liver, with compensatory hypertrophy of the contralateral liver (the FLR). Contraindications for PVE include portal vein thrombosis and severe portal hypertension.

Because HCC is supplied primarily by hepatic arterial flow, which increases after PVE, researchers have raised concerns about accelerated HCC growth after PVE. In addition, patients with cirrhosis have arterioportal shunts, which may limit the efficacy of PVE. To address these concerns, sequential transarterial chemoembolization (TACE) followed by PVE is proposed for patients with HCC. Yoo and colleagues evaluated 71 patients who underwent sequential TACE and PVE compared with 64 patients who underwent PVE alone before right hepatectomy for HCC [35]. The TACE-PVE group had markedly higher increases in FLR volume, a lower incidence of postoperative hepatic failure, and better OS. The authors hypothesized that the better survival resulted partly from an antineoplastic effect of TACE via occlusion of arterial flow to the tumor. Also, in a study of 36 patients undergoing liver resection after sequential TACE and PVE or PVE alone, Ogata and colleagues found that 83% of the patients in the TACE-PVE group had complete tumor necrosis in their resected specimens compared with only 6% of those in the PVE group ($p < 0.001$) [36]. Based on these data, patients with HCC and chronic liver disease who are candidates for major hepatectomy should be considered for sequential TACE and PVE (Fig. 13.7).

Intraoperative Considerations

The goals of surgical resection of HCC are to minimize the risk of intrahepatic recurrence and maximize preservation of the nontumoral hepatic parenchyma. Two important considerations are the role of anatomic versus nonanatomic resection and the width of the required surgical margin.

Intrahepatic recurrence of HCC is related to the presence of intrahepatic metastases, which occur via vascular invasion and lead to early recurrence within 2 years after resection, and multicentric carcinogenesis, which results in delayed recurrence. To address the risk of early recurrence of HCC owing to intrahepatic metastases, investigators proposed anatomic resection in the 1980s [37]. The aim of anatomic resection is to resect the segment or segments of the liver perfused by the portal vein branch supplying the HCC and thus eradicate potential micrometastases. In 1999, Imamura and colleagues compared 56 patients who underwent anatomic resection with 82 patients who underwent nonanatomic resection of HCC less than 5 cm in diameter and found that anatomic resection was associated with longer recurrence-free survival [38]. These results were confirmed in a more recent study at the University of Tokyo of Child-Pugh A patients undergoing resection of HCC 5 cm or smaller, in which 53 patients undergoing nonanatomic resection had higher local recurrence and shorter disease-free survival rates than did 156 patients undergoing anatomic resection [39].

In contrast, other authors have shown no difference in survival between anatomic and nonanatomic resection of HCC less than 5 cm [40, 41]. Cucchetti et al. observed that the beneficial effect of anatomic resection was limited to reduction of early recurrence (<2 years) of high-grade HCC with microvascular invasion [42]. These data suggest that the benefit of anatomic resection correlates with the risk of intrahepatic micrometastases and vascular invasion, which is directly related to larger tumor size.

In addition to anatomic resection, an important intraoperative consideration in patients with HCC is the necessary width of surgical margins. However, the literature on optimal resection margins is conflicted. Poon and coworkers analyzed 288 HCC patients who underwent resection with narrow (<1 cm) versus wide (≥1 cm) margins. Most of the intrahepatic recurrences they observed were in segments distant from the resection or in multiple segments [43]. The width of resection margins, provided they were negative, did not influence postoperative recurrence rates. Similarly, a study by Nara et al. of 570 patients undergoing resection of solitary HCC demonstrated that 165 patients with negative margins of 1 mm or less had recurrence-free survival rates similar to those in 374 patients who had margins greater than 1 mm, except among noncirrhotic patients with non-simple nodular type of morphology [44].

In a randomized trial of patients with solitary HCC, Shi and colleagues observed that patients with 2 cm margins had a 5-year OS rate of 75%, whereas patients with 1 cm margins had a 5-year OS rate of 49% ($p = 0.008$) [45]. Also, marginal recurrence occurred in 30% of the patients in the 1 cm group but none in the 2 cm group ($p = 0.001$). The goal of surgical resection of HCC with a 2 cm margin should be balanced with the need to preserve functional liver parenchyma.

Prognostic Factors for Hepatocellular Carcinoma After Hepatic Resection

In the American Joint Committee on Cancer staging system for HCC, determinants of the T1–T3 categories are number and size of tumors and vascular invasion. These important prognostic factors are supported by large surgical series on HCC (Table 13.2) [46–50].

Table 13.2 Results of surgical resection and prognostic factors for hepatocellular carcinoma

		%							
References	No. of patients	Cirrhosis	Major resection	Multiple tumors	Tumor size > 5 cm	Vascular invasion	Morbidity and mortality rates	Survival	Prognostic factors
Capussotti et al. (2005) [46]	216	100	21	22	31	43	Morbidity, 38.4; mortality, 8.3	5-year OS rate, 34.1; 5-year DFS rate, 25.2	Child-Pugh score, tumor size, vascular invasion, positive margin
Katz et al. (2009) [47]	192	32	60	11	79	60	Morbidity, 51	5-year OS rate, 41; 5-year recurrence rate, 76	Child-Pugh score, vascular invasion, positive margin, major hepatectomy, operative blood loss
Wang et al. (2010) [48]	438	N/A	11	15	62	19 (macroscopic)	Morbidity, 21.7; mortality, 7.5	5-year OS rate, 43.3; 5-year recurrence rate, 56.2	Child-Pugh score, size, vascular invasion, resection margin, capsular invasion
Fan et al. (2011) [49]	808	60	58	28	Median, 5.3 cm	49 (microscopic)	Morbidity, 24.8; mortality, 3.1	5-year OS rate, 54.8; 5-year DFS rate, 34.8	Vascular invasion, positive margin, multiple tumors, preoperative symptoms, postoperative complications
Kluger et al. (2014) [50]	313	47	56	20	65	24 (macroscopic) and 50 (microscopic)	Major morbidity, 5; mortality, 8	5-year OS rate, 67; 5-year DFS rate, 32	Vascular invasion, intraoperative transfusion, cirrhosis, poor differentiation, satellite lesions, AFP level > 200 ng/mL

OS Overall survival, *DFS* disease-free survival, *N/A* not available, *AFP* alpha-fetoprotein

Multicentric HCC is associated with high recurrence rates of 80–100% after partial hepatectomy. Thus, for cirrhotic patients with multiple tumors within the Milan criteria, liver transplantation is the best treatment option. For patients with multicentric HCC outside the Milan criteria, partial hepatectomy may be performed with satisfactory outcomes in selected patients. Ishizawa et al. demonstrated that the Child-Pugh score is an important determinant of survival after resection of multinodular HCC, with 5-year OS rates of 58% and less than 20% in patients with Child-Pugh A and B disease, respectively [33]. In that study, 75% of patients had intrahepatic recurrences, which were treated with repeat hepatic resection in nearly one-quarter of the patients.

Patients with HCC larger than 5 cm are generally not eligible for transplantation or ablation. Therefore, surgical resection is the preferred treatment option in such cases. However, larger tumors may be more technically challenging to resect than smaller ones and may require major hepatectomy. In addition, larger tumor size correlates with increased risk of vascular invasion, which independently predicts poor survival after resection. On the other hand, resection of solitary HCC larger than 5 cm without vascular invasion in patients with preserved hepatic function is associated with favorable outcomes. Data from the International Cooperative Study Group on HCC on 380 patients with large (>5 cm) or multinodular HCC demonstrated a 5-year OS rate of 39% and postoperative morbidity and mortality rates of 23.0% and 2.7%, respectively [51].

Vascular invasion is defined as macroscopic when it is visible radiologically and/or on gross examination, or microscopic. Both microscopic and macroscopic vascular invasions are independent predictors of recurrence and poor survival after resection of HCC. However, a study by Shindoh et al. demonstrated that microscopic vascular invasion in small HCC measuring 2 cm or less in diameter did not affect prognosis, with 5-year OS rates of 71.3% and 75.0%, with and without microvascular invasion, respectively ($p = 0.8$) [52]. In patients with HCC larger than 2 cm, however, microvascular invasion was a significant prognostic factor, as the 5-year OS rates were 47.3% and 61.4% in patients with and without microvascular invasion, respectively, ($p < 0.001$).

The prognosis for HCC with major vascular invasion is particularly poor, and the role of hepatic resection with invasion of a main portal or hepatic vein is controversial. Data from the International Cooperative Study Group on HCC on 102 HCC patients with major vascular invasion who underwent hepatic resection demonstrated a 5-year OS rate of only 10% [53]. A report by Ikai and colleagues demonstrated higher survival rates after resection of HCC with tumor invasion or thrombus in the second-order branches of the portal vein than after resection of those with tumor invasion or thrombus in the first-order branches or main portal vein trunk [54]. Similarly, patients undergoing resection of HCC with a tumor thrombus in a hepatic vein or branch had better survival than did patients with HCC with a thrombus in the inferior vena cava, which was associated with a 0% 2-year survival rate. Thus, resection may confer a survival benefit to HCC patients with macrovascular invasion involving distal portal and hepatic vein branches but is rarely indicated for those with invasion of the main portal vein trunk or inferior vena cava.

Conclusions

In patients with HCC who are not eligible for liver transplantation or ablation, surgical resection is the primary treatment provided hepatic reserve is sufficient. Portal hypertension is a contraindication for major hepatectomy, but selected patients may undergo minor resection provided they do not have ascites or a bilirubin level greater than 2 mg/dL. PVE is recommended for cirrhotic patients with FLR volumes less than 40% and may be combined with TACE to increase liver hypertrophy and induce tumor necrosis. Large surgical series demonstrated 5-year OS rates of 34–67% in HCC patients after hepatic resection, with postoperative mortality rates less than 10%. However, intrahepatic recurrence rates were high, up to 76% at 5 years after resection. Recurrence rates were higher in patients with multinodular HCC and vascular invasion than patients with solitary HCC without vascular invasion.

Role of Interventional Radiology for Hepatocellular Carcinoma

Image-guided locoregional therapies (LRTs) play key roles in the management of HCC. These therapies are used with palliative and curative intent, as a bridge to orthotopic liver transplant, before definitive therapy (surgical resection or orthotopic liver transplantation), or as the sole therapy or in a combined therapy in selected patients for whom surgical options are precluded [28, 55, 56]. Recent improvements in the field of interventional radiology are linked with enhanced outcomes of LRTs for HCC, thus increasing the attention paid to this therapeutic approach.

Transarterial Catheter-Based Therapies for Hepatocellular Carcinoma

Chemoembolization

Physicians first performed hepatic transarterial embolization for the treatment of HCC in the 1970s to improve local disease control. The rationale behind this approach relies on the

greater arterial density of HCCs than of the nontumorous hepatic parenchyma owing to the intense angiogenesis in HCCs during their progression. In TACE, first described in 1977 by Yamada [57], one or more chemotherapeutic drugs are added to an embolic agent because of a synergistic effect destroying the tumor tissue of the embolic agent and chemotherapeutic drugs. Several chemotherapeutic agents are used in TACE, the 2 most common being doxorubicin and cisplatin, which can be mixed with 1 or several different embolic agents. More recently, calibrated microparticles that can be loaded with chemotherapeutic drugs, namely drug-eluting beads (DEB-TACE), have gained acceptance in clinical practice. These drug-eluting microspheres allow for more reliable distal occlusion of small vessels and delivery of high-dose chemotherapy to a tumor with low systemic circulation of chemotherapeutic agents than do other TACE platforms (conventional TACE). A randomized phase 2 study (PRECISION V) comparing conventional TACE with DEB-TACE demonstrated a marked reduction in liver toxicity and serious adverse drug events and an insignificant trend of better antitumoral effect in the latter arm [58, 59].

Radioembolization with Yttrium-90

The term transarterial radioembolization is reserved for transarterial delivery of microspheres loaded with yttrium-90 (^{90}Y), a pure beta emitter with a physical half-life of 64.2 hours. Like other transarterial therapies, transarterial radioembolization relies on the preferential arterial supply and enhanced microvascular density of hepatic neoplasms [60, 61]. Acting as carriers, the biocompatible microspheres administered using this procedure can deliver radiation preferentially to tumors following hepatic artery delivery via microembolization in the tumor-related arterioles, creating an intense local radiotherapeutic effect that is proportional to the density of the microsphere distribution. Hence, unlike nonselective extracorporeal X-ray-based radiotherapy, transarterial radioembolization enables deposition of the particles predominantly within the tumor vasculature, leading to tumor damage while preserving the surrounding liver parenchyma. This critical feature allows for the delivery of radiation doses that are substantially higher than those that can be safely delivered via external-beam radiotherapy.

In the United States, two US Food and Drug Administration (FDA)-approved ^{90}Y microsphere products are in current use clinically: TheraSphere (MDS Nordion Inc., Kanata, Ontario, Canada), which consists of glass microspheres, and the resin-based SIR-Spheres (Sirtex Medical Ltd., Sydney, New South Wales, Australia). The glass ^{90}Y microspheres are approved for use in radiotherapy or as a neoadjuvant treatment with surgery or liver transplantation in patients with HCC under the auspices of an FDA humanitarian device exemption for orphan devices. The resin ^{90}Y microspheres have premarket approval for the treatment of hepatic metastases of primary colorectal cancers with adjuvant hepatic arterial infusion of floxuridine. However, globally, the regulatory approval of both products is more general, and they are commonly used for HCC therapy. The use of resin microspheres for an indication not included in the FDA-specific labeling is considered off-label use. Clinicians should consult and adhere to their institutional and regulatory agencies before prescribing off-label treatment with either type of microsphere.

Percutaneous Ablation

Percutaneous Ethanol Injection (PEI)

The injection of absolute ethanol inside and around a tumor using a guiding needle to induce coagulative necrosis as a result of cell dehydration and chemical occlusion of small vessels was the seminal technique for percutaneous ablation. Percutaneous ethanol injection (PEI) is a well-established technique for treating nodular HCCs with their induced necrosis rates that are intrinsically correlated with treated tumor size. Researchers have achieved complete necrosis in 90%, 70%, and 50% of HCCs measuring less than 2 cm, 2–3 cm, and 3–5 cm, respectively, using PEI [62–64]. Suboptimal response of larger tumors to PEI may be attributed to the presence of intratumoral septae and/or a capsule that blocks the diffusion of ethanol. Recently, the use of a multipronged injection needle (Quadra-Fuse; Rex Medical, Philadelphia, PA) for single-session PEI has resulted in sustained complete response rates (RRs) of 80–90% for HCCs measuring less than 4 cm [65].

Radiofrequency Ablation (RFA)

Radiofrequency ablation (RFA) has become the first-line choice for percutaneous ablation owing to its ability to induce complete necrosis in fewer sessions than with PEI, leading to better local disease control [66–70]. The frictional heat and movement of electrons within a lesion and surrounding tissues created by the delivery of an alternating electrical current within the lesion via an electrode needle placed directly into it generate heat in the immediate vicinity of the electrode that is then conducted to the surrounding environment, resulting in the coagulative necrosis of a finite tissue volume. The tissues surrounding an electrode needle tip are destroyed within seconds as temperatures reach 55–60 °C. The size and shape of the ablation zone vary depending on the amount of energy, type and number of electrodes, duration of ablation, and inherent tissue characteristics [71].

Owing to the efficacy and safety profile of RFA, its use has greatly expanded in the clinic, with 5-year survival outcomes comparable with those for hepatic resection [70].

The limitations of the technique include a heat-sink effect, whereby blood vessels adjacent to the tumor produce perfusion-mediated attenuation of thermal energy deposition, potentially leading to incomplete ablation, large (>5 cm) lesions, and tumor proximity to thermally sensitive structures, such as the gastrointestinal wall, gallbladder, diaphragm, and nerves.

Microwave Coagulation

Microwave (MW) ablation is an emerging hyperthermic ablative therapy that has gained attention as a valuable percutaneous ablation therapy for HCC. In MW ablation, the application of electromagnetic microwaves creates heat by agitating water molecules in the surrounding tissue, producing friction and heat and inducing cellular destruction via coagulative necrosis [72]. Compared with other available ablative technologies, MW ablation creates larger tumor ablation volumes with consistently higher intratumoral temperatures, has faster ablation times, and has a better convection profile [73], resulting in a reduction in the heat-sink effect created by vessels in proximity to the ablated zone [74]. Recent advances in MW engineering have resulted in better MW systems with the potential for creating more effective ablation zones.

Cryoablation

The subjection of tumors to freezing temperatures also can be used to cause tumor destruction by promoting local ischemia and disrupting the cellular membrane. In cryoablation, ice crystals form within tumor cells and the adjacent interstitium, causing cell dehydration and surrounding vascular thrombosis. Subsequently, when the tissues thaw, vascular occlusion leads to further ischemic injury [75]. Consistent tumor cell death is accomplished when the tissues are exposed to temperatures of at least −20 °C within an area of approximately 3 mm inside the margins of a cryoablation-induced ice ball, which is visible on computed tomography (CT) and magnetic resonance imaging (MRI) scans. As with RFA, the main limitations of cryoablation include proximity of an HCC to the blood vessels, gastrointestinal organs, nerves, and skin. Cryoablation of HCCs with large volumes can lead to the development of rare but serious systemic complications, such as cryoshock, a cytokine-mediated inflammatory response associated with coagulopathy and multiorgan failure, myoglobinuria, and severe thrombocytopenia [76–78].

Combination Therapies

The use of combination therapies for HCC, either different LRT combinations or LRTs combined with systemic therapies, has gained particular attention over the past decade. Combining different modalities of LRT, such as RFA and chemoembolization, may increase the treatment success rate, particularly for large HCCs [79]. The rationale for this approach lies in the devascularization of large HCCs via embolization or chemoembolization, which reduces the possibility of having a deleterious heat-sink effect in hypervascular tumors treated with RFA and thereby increases therapeutic effect. Several studies validated this approach by demonstrating larger ablation zones with the use of bland embolization or chemoembolization before the ablative treatment [80–82]. Moreover, performing RFA before chemoembolization can increase the deposition of chemoembolic agents in the periphery of an ablated tumor—the most common area of recurrence [83].

Also, researchers have suggested that the hypoxic environment within the tumor and its vicinity after TACE for HCC triggers the expression of neoangiogenic factors such as vascular endothelial growth factor (VEGF), possibly leading to tumor growth and progression. Therefore, to avoid the development of a neoangiogenesis cascade and, as a consequence, tumor progression, investigators have proposed using systemic therapies in the form of chemotherapy or antiangiogenic drugs with the intent of acting on different fronts of neoangiogenesis.

Locoregional Therapies for Hepatocellular Carcinomas According to the Barcelona Clinic Liver Cancer Staging System

Very Early Stage

Percutaneous hepatic ablation has become the standard therapeutic option in many institutions for HCCs smaller than 2 cm that are not subcapsular, perivascular, or adjacent to the gallbladder [55, 62, 84]. In a recent study, RFA was considered as effective as hepatic resection for the treatment of stage 0 HCC [85]. Another study demonstrated a complete RR of 97.2% and 5-year survival rate of 68% in 218 patients with very early-stage HCC treated using RFA [70]. Therefore, RFA is suggested by some authors as the best first-line therapy for very early-stage HCC, with surgical resection reserved for when individual patient variables render RFA unfeasible or unsafe [86]. In selected cases of very early-stage HCC, when surgery or RFA cannot be performed because of increased bilirubin levels, signs of portal hypertension, or risky tumor locations, such as pericholecystic lesions and lesions near the hilum, PEI still can be offered as an alternative.

Early Stage

Patients with solitary HCC or up to three lesions measuring less than 3 cm without any associated diseases are the ideal candidates for effective liver transplantation. For patients in

whom associated disease exists or for whom bridge therapy is desired before liver transplantation, percutaneous RFA is the modality of choice. Compared with PEI, RFA is consistently more effective and renders better local disease control. It also offers a greater survival benefit than does PEI as demonstrated in three independent meta-analyses that revealed 5-year survival rates of 51–64% in patients who met the Barcelona Clinic Liver Cancer (BCLC) criteria for surgical resection [85, 87, 88]. It consists of five stages of HCC: 0 (very early), A (early), B (intermediate), C (advanced), and D (terminal).

MW ablation is emerging as a viable alternative to RFA for patients with early-stage HCC owing to its larger tumor-ablation volumes, as the inherent characteristics of this technique are less influenced than those of RFA by the heat-sink effect created by vessels in proximity to a tumor. To date, the only randomized controlled trial comparing RFA and MW ablation for HCC did not reveal any differences in the effectiveness of the 2 techniques [89]. Nevertheless, recent advances in MW engineering along with improvements in the learning curve for this technology may result in a more effective ablation zone and better local disease control when compared with RFA.

Although not specified in the BCLC guidelines, combinations of ablative and transarterial treatments can be considered for an HCC case in which the target lesion measures from 3 to 5 cm in its longest axis in view of the suboptimal response of larger lesions to ablative therapies alone [80, 81, 90, 91]. The results of a recent randomized controlled trial assessing the efficacy of RFA combined with subsequent conventional TACE in patients with HCCs measuring 3.1–5.0 cm demonstrated that the rate of tumor progression was significantly lower in the combination group than in the ablation-only group (39% versus 6%; $p = 0.012$) [91]. In another study, DEB-TACE administered after RFA for HCC yielded a potential increase in treatment-induced necrosis [83]. Further studies to determine the ideal sequence of these techniques and the real impact of this approach are still required.

When percutaneous ablative therapies are not feasible or safe, TACE can be performed as an alternative. TACE can be a valuable tool in patients with solitary large (>5 cm) lesions for whom the benefits of combining different LRTs seem to be negligible.

Intermediate Stage (B)

TACE is the standard of care for BCLC-B HCC based on the improved survival rates demonstrated in a meta-analysis of six randomized clinical trials comparing TACE with best supportive care or suboptimal therapy [92]. Nevertheless, given the wide variability among patients classified as having intermediate-stage HCC with regard to tumor burden and liver functional status, not all patients will have the same benefits of TACE as demonstrated in a recent meta-analysis of randomized controlled trials [93]. In a recent study by Burrel et al., they observed a median survival duration of 42.8 months with the use of DEB-TACE in BCLC-B patients with HCC after censoring follow-up at the time of liver transplantation, sorafenib administration, and transarterial radioembolization [94]. Substratification of this patient population along with comparison of TACE with other LRTs and systemic therapies should be encouraged in future research. Also, a group investigated the use of radioembolization with Y^{90} in patients with intermediate- to advanced-stage HCC in a phase 2 study [95]. In that study, 17 patients with intermediate-stage HCC without portal vein thrombosis underwent lobar delivery of 120 Gy. Nine (53%) patients had a complete or partial response according to the European Association for the Study of the Liver criteria. Fifteen patients (88%) experienced disease control (complete response, partial response, or stable disease). The median time to progression (TTP) was 13 months, and median OS was 18 months (range, 12–38 months) [95]. In a recent multicenter trial assessing the use of radioembolization with Y^{90} in patients with HCC, 87 patients with BCLC-B HCC treated with Y^{90} had a median survival duration of 16.9 months (95% confidence interval, 12.8–22.8 months) [96]. Of note, this study demonstrated that radioembolization with Y^{90} appears to be particularly promising in patients with intermediate-stage HCC who are considered poor candidates for TACE (median OS range, 15.4–16.6 months) as well in those for whom prior TACE or bland embolization was ineffective (median OS duration, 15.4 months). The results of this study emphasized the possibility of using radioembolization as a complement to TACE in the HCC armamentarium.

Advanced Stage (C)

According to the BCLC guidelines, the use of the systemic multikinase inhibitor sorafenib is the cornerstone for advanced HCC [55] as demonstrated in two randomized control trials [97, 98] in which this new therapy was compared with a placebo. Although LRTs are not recommended for BCLC-C disease, many patients who undergo LRT in the form of TACE or radioembolization are in fact classified as having advanced-stage HCC. This subclass of patients is characterized by the presence of tumoral invasion of a branch vein with or without limited extrahepatic disease and a performance status of 1–2. Combination therapy using TACE and sorafenib is technically feasible and generally well tolerated in patients with unresectable HCC [99–101]. In a recent phase 2 study of concurrent conventional TACE and sorafenib, Park et al. demonstrated median times to progression of 7.3 months and 5.0 months in patients with BCLC-B and BCLC-C HCC, respectively [100]. This yielded longer times to progression in both groups than in patients who underwent conventional TACE alone (4.5 months and 2.8 months, respectively).

Concurrent therapy for HCC with DEB-TACE and sorafenib also has been a subject of investigation [101]. DEB-TACE increases serum aminotransferase levels to a lesser degree than does conventional TACE; it is the most common reason for delaying therapy with sorafenib. Of note, sorafenib should be administered as soon as possible after TACE to prevent an early surge in the expression of VEGF and other angiogenic factors. Pawlik et al. assessed the safety of and RR combination therapy with DEB-TACE and sorafenib in patients with advanced-stage HCC [101]. Their results demonstrated that the combination was well tolerated and safe and that most of the toxic effects related to sorafenib were manageable with dose adjustment.

The Modern Role of Radiotherapy for Hepatocellular Carcinoma

HCC is considered a radiosensitive disease, and radiotherapy may be used at all stages of the disease. Advances in the delivery of radiotherapy over the past decade have been rapid, improving its use in palliative and definitive treatments. Most notably, stereotactic body radiotherapy (SBRT) has become common for many types of cancer owing to its success against lung cancer. The application of this technique to HCC has been safe and effective, but the role of radiotherapy for HCC remains unclear because no randomized controlled trials have compared it with other therapies or supportive measures. Thus, physicians have generally adopted treatment algorithms based on the clinical presentations of HCC and their knowledge of the efficacy and limitations of other liver-directed therapies. We review the current roles of radiotherapy for HCC and point to future directions for it as follows:

A Brief History of Radiotherapy for Liver Cancer

Modern radiotherapy relies on three-dimensional (3D) imaging modalities such as CT and MRI. These techniques are used in the delineation of tumors, planning how to direct the radiation beams from a linear accelerator, and modeling the radiation dose to the tumor and normal tissue.

Prior to the implementation of 3D imaging for radiotherapy planning, radiologists used plain X-rays to design radiation fields, which provided very limited information on doses to the internal anatomy. This is partly why as recently as the 1980s radiotherapy was considered unsafe for the liver. Important studies on whole-abdominal irradiation for endometrial cancer and whole-liver irradiation for pancreatic cancer demonstrated that doses exceeding 30 Gy at 2–3 Gy per fraction could lead to liver failure [102]. However, seminal work demonstrated that high doses of radiation could be tolerated if given to partial volumes of the liver [103]. This series of studies also established objective parameters for evaluating the dose of radiation to the normal liver volume [104].

In the 1990s, a prospective evaluation demonstrated a radiotherapy response rate of 68% in 25 patients with hepatobiliary cancer or colorectal liver metastasis. The investigators demonstrated that the radiation dose was associated with both progression-free survival and OS. They delivered up to 90 Gy in 60 fractions, with the fractions given twice daily [105]. The median survival duration for the patients given 70 Gy or more was not reached in the initial study, and this helped inspire the development of better techniques to deliver high doses of radiation for liver cancers.

Modern Techniques of Delivering Radiotherapy for Liver Cancer

To deliver high doses of radiation for HCC and other liver cancers, a number of challenges must be overcome. These include the motion of the target owing to breathing and assurance that high doses are delivered to the correct places each day. Image-guided radiotherapy has advanced considerably, with multiple options emerging as solutions to the challenges to high-dose radiotherapy for HCC and other liver tumors.

Solutions for Organ Motion

Tracking

Liver tumor targets can be tracked in real time using implanted fiducials. One example is the ExacTrac® system (Brainlab AG, Munich, Germany), which uses multiple noncoplanar X-rays to track radiopaque fiducials implanted in or near a tumor. Automated computer algorithms provide alignment shifts for the radiation beams. For hypofractionated treatment of liver tumors, this method reportedly can track a moving target at an accuracy of within 1 mm [106]. Researchers have developed other real-time tracking systems as well [107–109]. Most linear accelerators include on-board imaging that enables fiducial-based alignment using orthogonal films or cone-beam CT.

Breath Hold

One way to reduce uncertainty about target location and reduce the irradiated healthy liver volume is to have the patient hold his or her breath during treatment delivery for several seconds at a time. Two examples of systems developed for this purpose are the Varian Real-time Position Management™ system (Varian Medical Systems, Inc., Palo Alto, California) and the Active Breathing Coordinator™

system (Elekta Instrument AB, Stockholm, Sweden). Interfractional variations in breath-hold position can exceed 4 mm [110, 111], which makes image-guided therapy an important addition to breath-hold techniques. The details regarding image guidance of radiotherapy are described as follows:

Gating

Respiratory gating is another method of accounting for the motion of liver tumors during radiotherapy [112]. This involves turning on the radiation beam during specified points in the breathing cycle. Successful use of gating techniques requires a regular breathing pattern; gating at end expiration is usually best because of less motion during that point in the respiratory cycle than other parts of the breathing cycle. Investigators have developed multiple methods to achieve gating, which are tied to either internal or external methods to monitor the organ or breathing pattern.

Abdominal Compression

Restricting the movement of the abdomen using a compression device can also minimize respiratory-associated motion. This method is commonly used while treating liver tumors with SBRT. The most common technique uses an abdominal compression plate that is placed 3–4 cm below the costal margin. The plate is connected to a load cell that can measure how much force is being applied to the abdomen. This device is usually used when the superior-inferior movement of the tumor exceeds 1 cm, but it also may be needed for tumors within 1 cm of the gastrointestinal tract [113]. Because compression plates can cause variable deformation of the liver, an alternative solution for liver tumors is the use of a pneumatic compression belt. Authors have reported that this emerging option reduces respiratory motion to less than 5 mm [114]. Notably, although compression does not require a regular breathing pattern, it only minimizes rather than eliminates organ motion and can move bowels closer to large or extrahepatic cancers.

Image Guidance

Minimizing or eliminating breathing motion during radiotherapy must be combined with some form of image guidance to ensure that the target volume is in the proper location. The options for this include two-dimensional (2D) X-ray scans taken from at least two angles, cone-beam CT, CT-on-rails, and MRI. Each has its advantages and drawbacks. For example, 2D X-rays do not provide soft tissue delineation but are generally efficient regarding alignment and treatment time. Three-dimensional image acquisition can provide some degree of soft tissue information at different resolutions (generally, cone-beam CT < CT-on-rails < MRI) but is more time-consuming and expensive than 2D methods and requires more advanced alignment techniques to match variations in target locations with the original radiation plan.

Modern Studies of Radiotherapy for Liver Cancers

The emergence of the image-guidance techniques described in the previous section has enabled the use of high doses of radiation for liver tumors using highly accurate and precise techniques, specifically SBRT. SBRT has emerged as an effective definitive therapy for HCC and other tumors. The experience with SBRT for liver cancer has mirrored many of the results of that with SBRT for lung cancer, in which delivery of 54 Gy in 3 fractions produced a 2-year local control rate of 95% for inoperable early-stage cancers [115]. Similarly, the use of SBRT for small liver metastases produced a 2-year local control rate of 92%. Because of concerns regarding radiation-induced liver disease in patients with HCC and underlying cirrhosis, investigators have taken an individualized approach to the design of the initial phase 1 trials. For example, one group prescribed radiation doses based on a normal tissue complication probability model [116]. Extension of SBRT to HCC and intrahepatic cholangiocarcinoma in a phase 1 trial produced a median OS duration of 11.7 months with no dose-limiting toxicities using a 6-fraction regimen [117].

Safely delivering SBRT to large liver tumors (>7 cm) has been challenging, however. For example, in a report on sequential phase 1 and 2 trials of SBRT for HCC in 102 patients who were not eligible for other LRTs (median tumor size 7 cm), the locoregional control rate at 1 year was good (87%), but the rate of at least grade 3 toxicity was high (30%), and 7 patients may have died of treatment-related causes [118].

Proton therapy has allowed for treatment of larger target volumes at larger doses per fraction as compared with the historical use of conventional photon therapy. Dosimetric and clinical studies have demonstrated that the irradiated liver volume is markedly lower with protons than with photons [119, 120]. This may be advantageous for patients who have advanced cirrhosis. Results of delivery of hypofractionated regimens (16–25 fractions) with ablative doses for large liver tumors are similar to those of surgical resection, with 5-year local tumor control rates of up to 90% and OS rates of up to 50% in some patients [121–123].

At the University of Texas MD Anderson Cancer Center, we have taken the approach of combining SBRT with the time-honored principle of fractionation (15–25 treatments) to achieve ablative doses of radiation for large liver tumors.

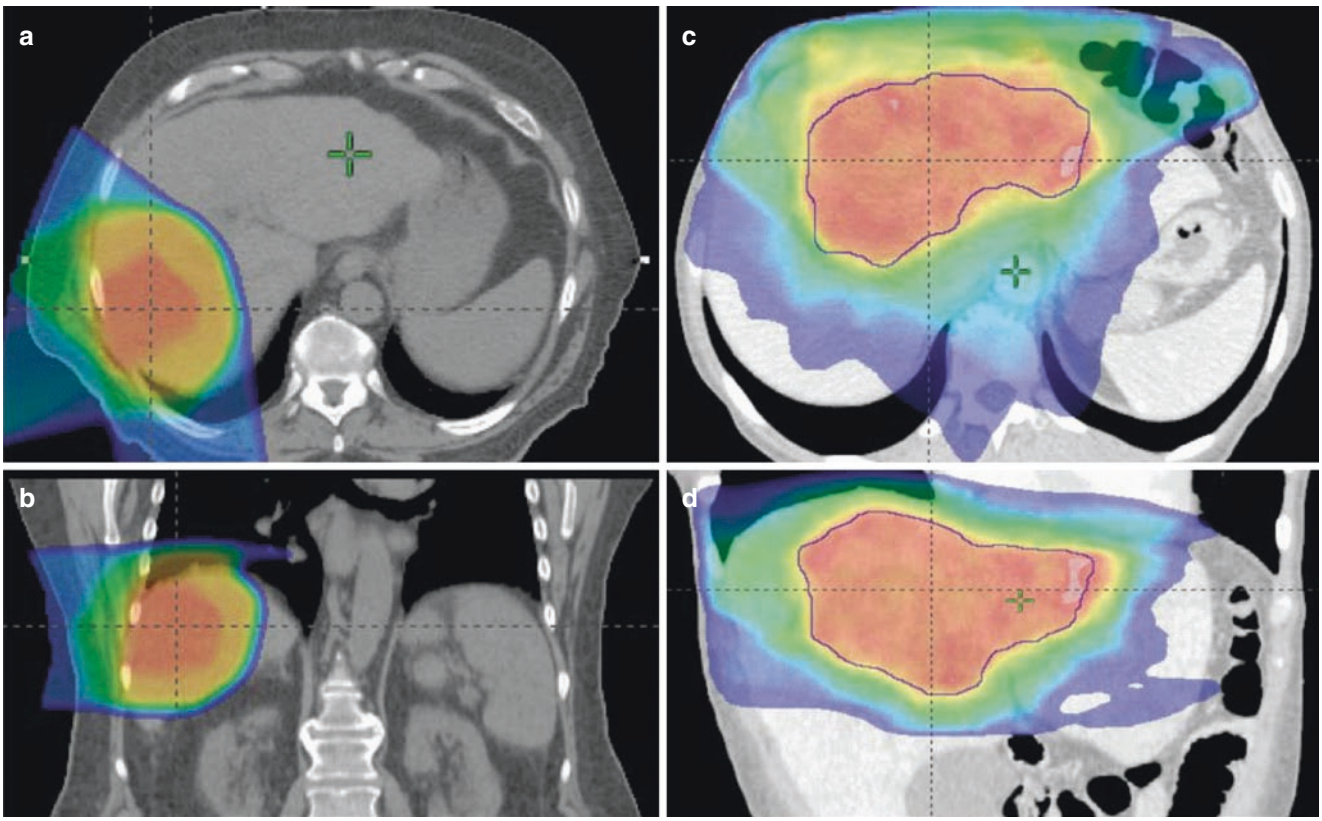


Fig. 13.8 Ablative proton therapy (**a**, axial view; **b**, coronal view) and intensity-modulated radiotherapy (**c**, axial view; **d**, coronal view) plans for patients with large liver tumors. The different colors represent different radiation doses, with the highest being red and the lowest being blue. Note: the low-dose distribution is different for protons and photons. (Reprinted with permission from Crane and Koay [125])

We have reported our results for intrahepatic cholangiocarcinoma [124] and are applying the same principles to HCC using either proton therapy or intensity-modulated radiotherapy [125]. Examples of plans for these two therapies are shown in Fig. 13.8 [125].

Radiotherapy for Advanced Hepatocellular Carcinoma

Palliation of Metastases and Tumor Thrombi

High rates of pain control (73–83%) can be achieved for bone metastases from HCC using radiotherapy. Similarly, physicians have achieved successful palliation of lung, brain, and nodal metastases of HCC [126–129]. For patients with portal vein tumor thrombi, the survival duration is usually shorter than 3 months. In this situation, authors reported that radiotherapy alone had high RRs and a median survival duration of 9.6 months [130]. External-beam irradiation is also feasible in combination with TACE for thrombi, resulting in 1-year survival rates as high as 73% in patients with Child-Pugh A cirrhosis [131].

Localized Hepatocellular Carcinoma and Advanced Cirrhosis

The risk of radiation-induced liver disease is high in patients with impaired liver function, such as advanced hepatic cirrhosis (Child-Pugh A6 or worse) or limited functional liver volumes because of prior therapies (chemotherapy and/or surgery). Reducing the risk of radiation-induced liver disease is of great interest for patients with advanced hepatic cirrhosis and HCC or other liver tumors. Successful achievement of this would provide a potentially curative treatment for these patients who otherwise have limited options.

A solution for delivery of radiotherapy for these patients includes liver single-photon emission CT with technetium-99m sulfur colloid, which can define functional liver parenchyma in patients with advanced cirrhosis [132–134]. This enables radiation oncologists to direct the beam placement for conformal radiotherapy and potentially achieve reduced hepatic toxicity (Fig. 13.9) [132]. Authors reported on the combination of this image-guided technique in a retrospective single-institution series [135]. At MD Anderson, we have an ongoing phase 1 trial evaluating the safety of high-dose

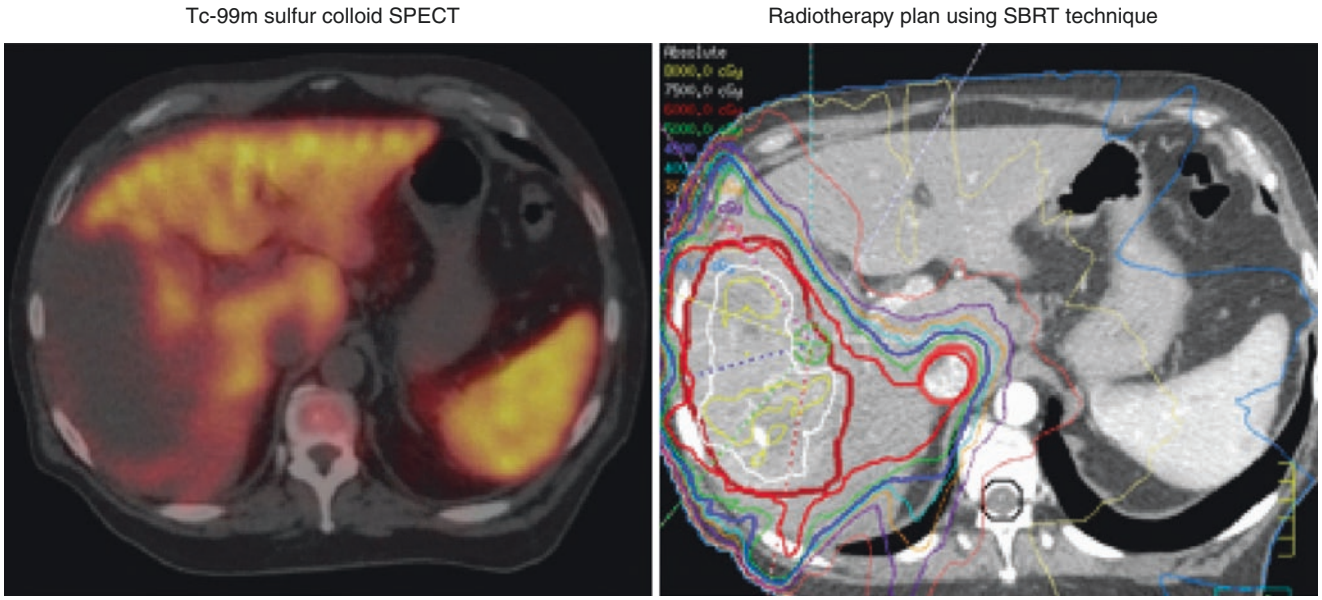


Fig. 13.9 Functional single-photon emission CT with technetium-99 m sulfur colloid enables identification of healthy livers and placement of radiation beams to avoid excess irradiation, especially in patients with locally advanced liver cancers and advanced cirrhosis. This patient for whom this scan was obtained had Child-Pugh B7 cirrhosis and a large right-sided HCC with an associated tumor thrombus that extended up the inferior vena cava. An intensity-modulated radiotherapy plan with a simultaneous integrated boost delivered a maximal dose of 75 Gy in 25 fractions and a microscopic dose of 45 Gy in 25 fractions to the patient

radiotherapy in patients with limited functional liver reserve and liver cancers, which is the first prospective evaluation of these techniques (Clinicaltrials.gov identifier NCT02626312).

Future Directions

The role of radiotherapy for HCC is expanding, and it should be considered for patients who are not appropriate candidates for liver-directed therapies such as surgery and TACE. Ongoing trials are addressing open questions about the role of SBRT, including what its role may be for patients who are candidates for liver transplantation, how effective it is in comparison with TACE and sorafenib, and whether it can be combined with other therapies to improve HCC outcomes. The role of proton therapy for HCC is also an open question, and future randomized studies will determine how conformal proton therapy compares with photon therapy.

Systemic Treatment of Hepatocellular Carcinoma

Basically, the treatment options for HCC fall into two categories: surgical and nonsurgical. Nonsurgical therapies include ablation, transarterial chemoembolization (TACE), irradiation, radioembolization Y-90, and systemic therapies. Treatment is determined according to disease stage, and many staging systems are available.

Several staging and prognostic systems have been developed to guide treatment of HCC. They include the TNM, Okuda, Cancer of the Liver Italian Program, and Barcelona Clinic (BCLC) staging systems. The BCLC system is the one used most.

Surgical options are curative for HCC. However, only about 15% of patients have surgical disease at diagnosis. Thus, a majority of HCC patients present with nonsurgical stage of their disease. Before the approval of sorafenib by the FDA for treatment of HCC, a globally approved standard systemic treatment of unresectable or metastatic HCC was lacking. Unfortunately, the prognosis for advanced or end-stage HCC is very poor, and the treatment options for it are limited. Generally, systemic chemotherapy or best supportive care is performed.

Systemic Chemotherapy

Despite the many different systemic chemotherapeutic agents and their combinations, standard systemic chemotherapy—either single-agent or combination—for HCC is lacking, and the effectiveness of systemic chemotherapy for it remains unclear.

No authors have reported that any systemic chemotherapy is better for HCC than single-agent doxorubicin, which has not conclusively improved survival rates over that with supportive care. Conventionally, chemotherapeutic regimens are either single agents (e.g., doxorubicin, mitoxantrone, fluoropyrimidines, gemcitabine, irinotecan, thalidomide) or combinations (cisplatin-, gemcitabine-, or oxaliplatin-based

or the combination of cisplatin, interferon α[alpha]-2b, doxorubicin, and fluorouracil). Unfortunately, randomized controlled trials have not demonstrated that any chemotherapeutic regimens improved overall survival rates for HCC over those with best supportive care [136–138].

Single-Agent Chemotherapies

As described previously, doxorubicin has been the most studied chemotherapeutic agent for advanced-stage HCC. Its effects on HCC have been known since the 1970s. However, few trials have demonstrated an objective RR for doxorubicin greater than 20% [139].

Fluoropyrimidines (5-Fluorouracil and Capecitabine)

The drug 5-fluorouracil (5-FU) has acceptably low toxicity and extensive antitumoral activity. This drug is a pyrimidine analog reported to be the first chemotherapeutic agent used in treatment of HCC. RRs for bolus 5-FU monotherapy for HCC are low, and objective RRs have ranged from 10% to 28% [140–143]. Low overall RRs (~10%) and short median survival durations (3–5 months) have discouraged further use of 5-FU as a single agent for treatment of HCC [144, 145].

Capecitabine is an oral prodrug of 5-FU that is metabolized to 5-FU in a three-step enzymatic reaction. The last enzyme is thymidine phosphorylase, which converts prodrug to the active drug form in the tumor [146]. Capecitabine is used in both conventional chemotherapy and metronomic chemotherapy for HCC. When given alone, capecitabine is well tolerated and delays and reduces the risk of tumor recurrence [147].

Gemcitabine given as single-agent chemotherapy for advanced HCC has been evaluated in several phase 2 trials. Unfortunately, the results were not promising [148–150].

Investigators have studied irinotecan and thalidomide in the treatment of advanced HCC, as well. Use of single-agent irinotecan and thalidomide has not produced significant results in patients with advanced HCC [151, 152].

Despite some preclinical trials suggesting that taxanes are useful in treatment of HCC, satisfactory data supporting this are lacking [153, 154].

Cisplatin has modest efficacy against advanced-stage HCC (RR 15%). It is not recommended for use as a single agent in treatment of advanced HCC, but it is being used intra-arterially in local therapy for it [155].

Combination Chemotherapy Regimens

As described previously, researchers have studied many combinations of chemotherapeutic agents in patients with advanced HCC, obtaining results that were not more promising than those for single agents [156–164]. However, these combinations have yet to be studied in comparison with best supportive care.

Epirubicin, Cisplatinum, and Infusional 5-Fluorouracil

Investigators studied this combination in patients with HCC who were not able to undergo surgical, intra-arterial, or percutaneous treatment. The results were poor, and survival rates were low [161].

Capecitabine and Cisplatin

The use of this combination did not increase OS for HCC over that of doxorubicin alone [165, 166].

Gemcitabine and Doxorubicin

The RR for this regimen in HCC patients was not higher than that for other combinations [159]. Over the years, doxorubicin and gemcitabine have been relatively effective against HCC. Researchers have studied pegylated liposomal doxorubicin and gemcitabine in patients with advanced HCC, the results of which were encouraging [167].

Gemcitabine and Oxaliplatin

These two agents seem to be well tolerated and active in patients with advanced HCC, especially those with underlying nonalcoholic liver disease [168].

Oxaliplatin, 5-Fluorouracil, and Leucovorin

In a comparison of this combination with doxorubicin in HCC patients, the OS rate, progression-free survival rate, and RR were encouraging [169].

Cisplatin, Interferon α(Alpha)-2b, Doxorubicin, and 5-Fluorouracil

In some trials using this regimen, researchers highlighted the importance of HCC patient selection. Specifically, the results were worse for patients who had cirrhotic livers than for those with normal livers. The regimen showed a promising activity as a neoadjuvant strategy in a recent study that selected potentially resectable cases with no cirrhosis. However, this approach needs to be validated independently [170, 171].

Molecularly Targeted Therapy

As pointed out earlier, systemic chemotherapies for advanced HCC have not been promising; only a few agents had RRs greater than 20%, and none of them demonstrated convincing survival benefits in phase 3 studies. The majority of patients with HCC have cirrhotic livers, which cause decreased hepatic reserves and complications that may compromise effective delivery of systemic chemotherapy.

HCC has a very poor prognosis and a chemotherapy-resistant nature. Researchers have suggested that some factors that lead to treatment resistance of HCC include expression of the multidrug resistance gene, glutathione *S*-transferase, and heat shock proteins; mutations of p53; and consequent high-level expression of P-glycoprotein [172].

Preclinical and clinical studies have demonstrated that progression of human HCC is associated with angiogenesis and that high microvascular density in HCCs is associated with poor prognosis [173]. Angiogenesis and signaling via RAF, mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), and MAPK cascades are reported to play important roles in the development of HCC [174]. Because of the insufficiency of systemic chemotherapy for HCC, researchers have examined some molecularly targeted agents that specifically target these pathways and discovered that they can be used to treat HCC (Table 13.3) [97, 98, 138, 139, 141, 150, 169–171, 175–190].

Table 13.3 The most important clinical trials and their results in hepatocellular carcinoma

The drug used in HCC treatment	Pharmacologic category	Mechanism of action	Study phase	Study year	Outcome	References
Doxorubicin (Adriamycin)	Anthracycline	Inhibits topoisomerase II	2	Olweny et al. (1975)	mOS, 8 m	[139]
5-Fluorouracil (5-FU)	Antimetabolite (pyrimidine analog)	Inhibits thymidylate synthetase	2	Tetef et al. (1995)	TTP, 2.7 m mOS, 3.8 m	[141]
Gemcitabine	Antimetabolite (pyrimidine analog)	Inhibits DNA polymerase	2	Yang et al. (2000)	TTP, 3.0 m mOS, 4.6 m	[150]
Doxorubicin and cisplatin	Anthracycline and alkylating agent	Inhibits topoisomerase II, covalently binds to DNA bases, and disrupts DNA function, respectively	2	Lee et al. (2004)	TTP, 6.6 m mOS, 7.3 m	[175]
Gemcitabine and cisplatin	Antimetabolite (pyrimidine analog) and alkylating agent	Inhibits DNA polymerase, covalently binds to DNA bases, and disrupts DNA function, respectively	2	Parikh et al. (2005)	TTP, 4.5 m mOS, 5.3 m	[176]
Gemcitabine plus oxaliplatin	Antimetabolite (pyrimidine analog) and alkylating agent	Inhibits DNA polymerase, covalently binds to DNA bases, and disrupts DNA function, respectively	Retrospective multicenter study	Zaanan et al. (2013)	TTP, 8 m mOS, 11 m	[177]
Oxaliplatin plus short-term infusional 5-FU and leucovorin versus single-agent doxorubicin	Antimetabolite (pyrimidine analog), alkylating agents, anthracycline	Inhibits thymidylate synthetase, covalently binds to DNA bases, disrupts DNA function, and inhibits topoisomerase II	3	Qin et al. (2014)	mOS, 6.40 m TTP, 2.93 m versus mOS, 4.97 m TTP, 1.77 m	[169]
PIAF (Cisplatin, interferon α(alpha)-2b, doxorubicin, and infusional 5-FU)	Alkylating agents, immunomodulator, anthracycline, antimetabolite (pyrimidine analog), respectively	Covalently binds to DNA bases and disrupts DNA function, binds to specific receptors on the cells to initiate activity, inhibits topoisomerase II, and inhibits thymidylate synthetase, respectively	2	Leung et al. (1999) and Kaseb et al. (2013)	mOS, 8.9 m RR, 26% and RR, 36% versus 15% mOS, 21.3 m versus 13.6 m	[171, 178]
Cisplatin, interferon α(alpha)-2b, doxorubicin, and infusional 5-FU versus doxorubicin	Alkylating agents, immunomodulator, anthracycline, antimetabolite (pyrimidine analog), respectively	Covalently binds to DNA bases and disrupts DNA function, binds to specific receptors on the cells to initiate activity, inhibits topoisomerase II, and inhibits thymidylate synthetase, respectively	3	Yeo et al. (2005)	mOS, 8.67 m RR, 20.9% versus mOS, 6.83 RR, 10.5%	[170]
Sorafenib versus placebo (SHARP)	VEGF inhibitor	Inhibits multiple kinases (VEGFR-1, VEGFR-2, and VEGFR-3; PDGFRβ[beta]; cKIT; FLT3; RET; CRAF; BRAF)	3	Llovet et al. (2008)	TTP, 5.5 m mOS, 10.7 m versus TTP, 2.8 m mOS, 7.9 m	[97]

Table 13.3 (continued)

The drug used in HCC treatment	Pharmacologic category	Mechanism of action	Study phase	Study year	Outcome	References
Sorafenib versus placebo (Asia-Pacific)	VEGF inhibitor	Inhibits multiple kinases (VEGFR-1, VEGFR-2, and VEGFR-3; PDGFRβ[beta]; cKIT; FLT3; RET; CRAF; BRAF)	3	Cheng et al. (2009)	TTP, 2.8 m mOS, 6.5 m versus TTP, 1.4 m mOS, 4.2 m	[98]
Doxorubicin plus sorafenib versus doxorubicin plus placebo	Anthracycline and VEGF inhibitor, respectively	Inhibits topoisomerase II and multiple kinases (especially VEGFs)	2	Abou-Alfa et al. (2010)	TTP, 6.4 m mOS, 13.7 m versus TTP, 2.8 m mOS, 6.5 m	[179]
Bevacizumab	Monoclonal antibody	Inhibits VEGF	2	Siegel et al. (2008)	mOS, 12.4 m	[180]
Sunitinib versus sorafenib	VEGF inhibitor	Inhibits multiple kinases (VEGFR-1, VEGFR-2, and VEGFR-3; PDGFRβ[beta]; cKIT; FLT3; RET; CRAF; BRAF)	3	Cheng et al. (2013)	TTP, 3.8 m mOS, 7.9 m versus TTP, 4.1 m mOS, 10.2 m	[181]
Axitinib	VEGF inhibitor	Selectively inhibits VEGFR-1, VEGFR-2, and VEGFR-3	2	McNamara et al. (2015)	mOS, 7.1 m	[182]
Erlotinib plus sorafenib versus placebo plus sorafenib (SEARCH)	Epidermal growth factor receptor inhibitor and VEGF inhibitor, respectively	Inhibits HER1/epidermal growth factor receptor via tyrosine kinase activity and multiple kinases (especially VEGFR), respectively	3	Zhu et al. (2015)	TTP, 3.2 m mOS, 9.5 m versus TTP, 4.0 m mOS,8.5 m	[183]
Bevacizumab and erlotinib	Monoclonal antibody, epidermal growth factor receptor inhibitor	Inhibits VEGF and HER1/epidermal growth factor receptor via tyrosine kinase activity	2	Thomas et al. (2009)	mPFS, 9.0 m mOS, 15.6 m	[138, 184–186]
				and Kaseb et al. (2012)	and mPFS, 7.2 m mOS, 13.7 m	
				Kaseb et al. (2016)	mPFS, 3.9 m mOS, 9.9 m	
				and Johnson et al. (2013)	and mPFS,3 m mOS,9.5 m	
Brivanib versus placebo	VEGF inhibitor	Inhibits VEGFR-1, VEGFR-2, and VEGFR-3 and fibroblast growth factor receptor-1	3	Llovet et al. (2013)	TTP, 4.2 m mOS, 9.4 m versus TTP, 2.7 m mOS, 8.2 m	[187]
Everolimus versus placebo	mTOR kinase inhibitor	Inhibits mTOR	3	Zhu et al. (2014)	TTP, 3.0 m mOS, 7.6 m versus TTP, 2.6 m mOS, 7.3 m	[188]
Tivantinib versus placebo	c-MET inhibitor	Selectively inhibits c-MET	2	Santoro et al. (2013)	TTP, 1.6 m mOS, 6.6 m versus TTP, 1.4 m mOS, 6.2 m	[189]
Nivolumab versus placebo	Anti-PD-1 monoclonal antibody	Binds to the PD-1 receptor to block PD-L1 and PD-L2 from binding	1/2	El-Khoueiry et al. (2015)	RR, 42% mOS, 72% at 6 months	[190]

PFS Progression-free survival, *OS* overall survival, *RR* response rate, *TTP* time to progression, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor

Sorafenib

Sorafenib is a novel molecularly targeted agent that inhibits the serine/threonine Raf kinases and members of the cell surface kinase receptor family VEGF receptor (VEGFR-1, VEGFR-2, and VEGFR-3), the cell surface kinase receptor platelet-derived growth factor receptor (PDGFR), and tumorigenic receptor tyrosine kinases (RET, Fms-like tyrosine kinase-3 [FLT3], and c-Kit) [98]. Sorafenib was the only systemically administered agent to demonstrate a statistically significant, albeit minor, OS benefit for HCC in 2 large randomized, placebo-controlled phase 3 trials conducted in Western and Asian-Pacific populations. These similar trials focused on the effects of sorafenib on HCC and were conducted at the same time in different populations. The Western trial demonstrated that the time to progression (TTP) improved from 2.8 months to 5.5 months and that the mean OS duration improved from 7.9 months to 10.7 months in the placebo and sorafenib arms, respectively. Since that study, sorafenib received approval by FDA as a first-line treatment option for advanced-stage HCC [97, 98, 191].

Regorafenib

Regorafenib is a multikinase inhibitor that inhibits VEGF receptors 1–3, KIT, PDGFR-alpha and PDGFR-beta, RET, FGF receptors 1–2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, SAPK2, and PTK5 [192]. Since sorafenib's approval as the only front-line standard-of-care systemic therapy for unresectable HCC in 2007, multiple phase 3 trials assessing novel systemic drugs have failed to improve outcome against best supportive care in the second-line setting following sorafenib failure [187, 188, 193, 194]. Therefore, the positive outcome achieved with regorafenib therapy is a major development in the second-line systemic therapy setting after it reached its OS endpoint per the RESORCE study, which was conducted among patients who discontinued sorafenib because of evidence of progressive disease on imaging studies. Of note, patients who were intolerant of sorafenib or discontinued sorafenib because of side effects were excluded. Regorafenib improved the median OS to 10.6 months as compared to 7.8 months in the placebo arm with a hazard ratio of 0.63 (95% CI, 0.50–0.79; one-sided $p < 0.0001$). Additionally, median progression-free survival (PFS) was 3.1 in the regorafenib arm versus 1.5 months in the placebo/best supportive care arm, in favor of regorafenib, along with a significant intergroup difference in the disease control rate (DCR), which was 65.2% in the regorafenib arm and 36.1% in the placebo arm [195]. Subsequently, regorafenib was approved for use in the United States by the FDA in May 2017.

Sunitinib

Sunitinib inhibits multiple receptor tyrosine kinases; PDGFRα(alpha) and PDGFRβ(beta); VEGFR-1, VEGFR-2, and VEGFR-3; the stem cell factor receptor KIT; and FLT3. As a result, it exhibits antitumor and antiangiogenic activities [196]. The initial trial examining the safety and efficacy of sunitinib in patients with advanced HCC demonstrated unacceptable toxicity [197]. Therefore, investigators used a modified dose of sunitinib (37.5 mg/day) and observed modest antitumor activity in patients with advanced HCC, with manageable adverse effects [198]. Another study comparing this modified dose of sunitinib with sorafenib demonstrated that sunitinib was not superior or equivalent but rather markedly inferior to sorafenib [181].

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting the activity of VEGF-A [184]. It is an effective treatment option for, and well tolerated in, patients with advanced HCC even when given alone [180]. Researchers have studied bevacizumab combined with cytotoxic and targeted therapeutic agents (gemcitabine and oxaliplatin, capecitabine and oxaliplatin, and erlotinib) [138, 186, 199–201]. The combinations of bevacizumab with (1) gemcitabine and oxaliplatin and (2) capecitabine and oxaliplatin appeared to have a signal of activity and safety. Finally, bevacizumab and erlotinib combinations were tested in both front-line and second-line settings with conflicting results based on patient population, but showed signals of activity and safety as well [185, 202]. However, these results of bevacizumab studies in HCC need validation through further investigation of these combinations in HCC patients, possibly combined with other targeted agents and immunotherapy strategies [203–205].

Axitinib

Axitinib is a potent oral multitargeted tyrosine kinase receptor inhibitor and small-molecule indazole derivative [206, 207]. Investigators studied the efficacy of axitinib in HCC patients and found that it had encouraging tolerable clinical activity [182].

Brivanib

Brivanib is an ATP-competitive inhibitor of human VEGFR-1, VEGFR-2, and VEGFR-3 [208, 209]. After demonstrating effectiveness against HCC in a preclinical trial,

researchers used brivanib in first- and second-line single-agent and combination therapy for advanced HCC. Its antitumor activity was promising, and it had a manageable safety profile in patients with advanced disease [210]. In a comparison of brivanib with sorafenib, the TTP, objective RR, and disease control rate were similar [186].

Mammalian Target of Rapamycin-Based Therapy

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that regulates cell growth and proliferation. It belongs to the phosphatidylinositol 3-kinase–related kinase protein family. Everolimus is an mTOR inhibitor that was evaluated in patients with HCC in a phase 3 trial. In that study, it failed to improve OS and progression-free survival over that with treatment with a placebo [188, 211].

Immunotherapy (Immune Checkpoint Inhibitors)

After the valuable discovery that human cancer cells express cancer-associated antigens, researchers focused on the development of immunotherapies to mediate tumor regression. As a result, investigators recently found blockade of immune checkpoints to be one of the most promising approaches to activation of antitumor immunity. Cytotoxic T lymphocyte-associated molecule-4, programmed cell death protein (PD)-1, and PD ligand (PD-L) have been targets in treatment of various tumors as immune checkpoints. Cytotoxic T lymphocyte-associated molecule-4 is a cell surface molecule that is expressed almost exclusively on $CD4^+$ and $CD8^+$ T cells. This molecule has an essential role in the regulation of T-cell immune responses, especially in the maintenance of T-cell homeostasis [144, 212–214].

Tumor expression of PD-L1 may evade normal immune attack by exploiting the PD-1 immune checkpoint pathway. Both PD-L1 and PD-L2 bind to the PD-1 receptor on activated T cells, thus inhibiting T cells and T-cell attack [2]. A recent report demonstrated that patients with higher intratumoral expression of PD-L1 had markedly poorer prognoses than did patients with lower expression of it [215].

Trials of tremelimumab (an anti-cytotoxic T lymphocyte-associated molecule-4 monoclonal antibody), nivolumab (an anti-PD-1 antibody), and OX40 (a member of the tumor necrosis factor receptor superfamily) demonstrated very promising results in patients with advanced HCC [2, 190, 216–224].

The most promising data came from the study in which patients were treated with nivolumab (CheckMate-040). According to the interim results of the study, among 214 patients, the objective response rate was 16%, which included complete response in 2 (1%) patients and partial response in 33 (15%) patients. Additionally, stable disease was obtained in 111 patients and the overall response rate reached to 69%, which was a very striking rate. OS rates for all patients at 6 and 9 months were 82.5% and 70.8%, respectively. The study showed durable objective responses across all etiologic cohorts, which include HBV and HCV infection and manageable safety of nivolumab in patients with HCC. Data indicate activity across all etiologic subtypes and supporting ongoing study of nivolumab in HCC [225].

MET Inhibitors

Researchers have suggested that MET signaling has a role in the treatment of HCC. Therefore, some of them have performed investigations of MET signaling inhibition. Some clinical trials have had encouraging results for treatment with cabozantinib, crizotinib, onartuzumab, tivantinib, and rilotumumab [189, 226, 227].

Mitogen-Activated Protein Kinase Kinase Inhibitors

As described previously the RAS/RAF/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathway is a predominant signaling cascade in cell proliferation and carcinogenesis [228]. This pathway is activated in 50–60% of HCCs and is a potential target for therapy [229, 230]. Refametinib and selumetinib are orally administered inhibitors of mitogen-activated protein kinase kinase tyrosine kinase activity used in the treatment of advanced HCC [174, 231].

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in globocan 2012. Int J Cancer. 2015;136(5):E359–86.
2. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-pd-l1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–65.
3. Custer B, Sullivan SD, Hazlet TK, Iloeje U, Veenstra DL, Kowdley KV. Global epidemiology of hepatitis b virus. J Clin Gastroenterol. 2004;38(10 Suppl 3):S158–68.
4. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132(7):2557–76.
5. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis b virus DNA level. JAMA. 2006;295(1):65–73.

6. Ayub A, Ashfaq UA, Haque A. Hbv induced hcc: major risk factors from genetic to molecular level. Biomed Res Int. 2013;2013:810461.
7. El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011;365(12):1118–27.
8. Lavanchy D. Hepatitis b virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat. 2004;11(2):97–107.
9. Beasley RP. Hepatitis b virus. The major etiology of hepatocellular carcinoma. Cancer. 1988;61(10):1942–56.
10. Poon RT, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. J Am Coll Surg. 2002;194(5):592–602.
11. Yeh CN, Lee WC, Chen MF. Hepatic resection and prognosis for patients with hepatocellular carcinoma larger than 10 cm: two decades of experience at chang gung memorial hospital. Ann Surg Oncol. 2003;10(9):1070–6.
12. Theise N, Curado M, Franceschi S, Hytiroglou P, Kudo M, Park Y, et al. In who classification of tumors of the digestive system. In: Bosman F, Carneiro F, Hruban H, Theise N, editors. Hepatocellular carcinoma. 4th ed. Lyon: IARC; 2010.
13. Ishak K, Goodman Z, Stocker J. In tumors of the liver and intrahepatic bile ducts. In: Ishak K, Goodman Z, Stocker J, editors. Hepatocellular carcinoma. 3rd ed. Washington, DC: Armed Forces Institute of Pathology; 2001. p. 199–245.
14. Coston WM, Loera S, Lau SK, Ishizawa S, Jiang Z, Wu CL, et al. Distinction of hepatocellular carcinoma from benign hepatic mimickers using glypican-3 and cd34 immunohistochemistry. Am J Surg Pathol. 2008;32(3):433–44.
15. Shahid M, Mubeen A, Tse J, Kakar S, Bateman AC, Borger D, et al. Branched chain in situ hybridization for albumin as a marker of hepatocellular differentiation: evaluation of manual and automated in situ hybridization platforms. Am J Surg Pathol. 2015;39(1):25–34.
16. Evason KJ, Grenert JP, Ferrell LD, Kakar S. Atypical hepatocellular adenoma-like neoplasms with beta-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas. Hum Pathol. 2013;44(5):750–8.
17. Kakar S, Gown AM, Goodman ZD, Ferrell LD. Best practices in diagnostic immunohistochemistry: hepatocellular carcinoma versus metastatic neoplasms. Arch Pathol Lab Med. 2007;131(11):1648–54.
18. Abou-Alfa GKPT, Shindoh J, Vauthey J-N. Liver. In: Amin MBES, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. Ajcc cancer staging manual. 8th ed. New York: Springer; 2017. p. 287–93.
19. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346(16):1221–31.
20. Tateishi R, Okanoue T, Fujiwara N, Okita K, Kiyosawa K, Omata M, et al. Clinical characteristics, treatment, and prognosis of non-b, non-c hepatocellular carcinoma: a large retrospective multicenter cohort study. J Gastroenterol. 2015;50(3):350–60.
21. Kew MC. Epidemiology of hepatocellular carcinoma in subsaharan africa. Ann Hepatol. 2013;12(2):173–82.
22. Nagasue N, Ito A, Yukaya H, Ogawa Y. Androgen receptors in hepatocellular carcinoma and surrounding parenchyma. Gastroenterology. 1985;89(3):643–7.
23. Nagasue N, Ito A, Yukaya H, Ogawa Y. Estrogen receptors in hepatocellular carcinoma. Cancer. 1986;57(1):87–91.
24. Eagon PK, Elm MS, Epley MJ, Shinozuka H, Rao KN. Sex steroid metabolism and receptor status in hepatic hyperplasia and cancer in rats. Gastroenterology. 1996;110(4):1199–207.
25. Ostrowski JL, Ingleton PM, Underwood JC, Parsons MA. Increased hepatic androgen receptor expression in female rats during diethylnitrosamine liver carcinogenesis. A possible correlation with liver tumor development. Gastroenterology. 1988;94(5 Pt 1):1193–200.
26. Tejura S, Rodgers GR, Dunion MH, Parsons MA, Underwood JC, Ingleton PM. Sex-steroid receptors in the diethylnitrosamine model of hepatocarcinogenesis: modifications by gonadal ablation and steroid replacement therapy. J Mol Endocrinol. 1989;3(3):229–37.
27. Nakatani T, Roy G, Fujimoto N, Asahara T, Ito A. Sex hormone dependency of diethylnitrosamine-induced liver tumors in mice and chemoprevention by leuprorelin. Japanese J Cancer Res: Gann. 2001;92(3):249–56.
28. Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–2.
29. Mazzaferro V, Lencioni R, Majno P. Early hepatocellular carcinoma on the procrustean bed of ablation, resection, and transplantation. Semin Liver Dis. 2014;34(4):415–26.
30. Munene G, Vauthey JN, Dixon E. Summary of the 2010 ahpba/sso/ssat consensus conference on hcc. Int J Hepatol. 2011;2011:565060.
31. Teh SH, Christein J, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model of end-stage liver disease (meld) score predicts perioperative mortality. J Gastrointest Surg. 2005;9(9):1207–15; discussion 1215.
32. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, La Barba G, et al. Impact of model for end-stage liver disease (meld) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl. 2006;12(6):966–71.
33. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology. 2008;134(7):1908–16.
34. Palavecino M, Chun YS, Madoff DC, Zorzi D, Kishi Y, Kaseb AO, et al. Major hepatic resection for hepatocellular carcinoma with or without portal vein embolization: perioperative outcome and survival. Surgery. 2009;145(4):399–405.
35. Yoo H, Kim JH, Ko GY, Kim KW, Gwon DI, Lee SG, et al. Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization only before major hepatectomy for patients with hepatocellular carcinoma. Ann Surg Oncol. 2011;18(5):1251–7.
36. Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. Br J Surg. 2006;93(9):1091–8.
37. Makuuchi M, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. Surg Gynecol Obstet. 1985;161(4):346–50.
38. Imamura H, Matsuyama Y, Miyagawa Y, Ishida K, Shimada R, Miyagawa S, et al. Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. Br J Surg. 1999;86(8):1032–8.
39. Shindoh J, Makuuchi M, Matsuyama Y, Mise Y, Arita J, Sakamoto Y, et al. Complete removal of the tumor-bearing portal territory decreases local tumor recurrence and improves disease-specific survival of patients with hepatocellular carcinoma. J Hepatol. 2016;64(3):594–600.
40. Kang CM, Choi GH, Kim DH, Choi SB, Kim KS, Choi JS, et al. Revisiting the role of nonanatomic resection of small (< or = 4 cm) and single hepatocellular carcinoma in patients with well-preserved liver function. J Surg Res. 2010;160(1):81–9.
41. Dahiya D, Wu TJ, Lee CF, Chan KM, Lee WC, Chen MF. Minor versus major hepatic resection for small hepatocellular carcinoma (hcc) in cirrhotic patients: a 20-year experience. Surgery. 2010;147(5):676–85.

42. Cucchetti A, Qiao GL, Cescon M, Li J, Xia Y, Ercolani G, et al. Anatomic versus nonanatomic resection in cirrhotic patients with early hepatocellular carcinoma. Surgery. 2014;155(3):512–21.
43. Poon RT, Fan ST, Ng IO, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. Ann Surg. 2000;231(4):544–51.
44. Nara S, Shimada K, Sakamoto Y, Esaki M, Kishi Y, Kosuge T, et al. Prognostic impact of marginal resection for patients with solitary hepatocellular carcinoma: evidence from 570 hepatectomies. Surgery. 2012;151(4):526–36.
45. Shi M, Guo RP, Lin XJ, Zhang YQ, Chen MS, Zhang CQ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007;245(1):36–43.
46. Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, Massucco P. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival--a european single center experience. Eur J Surg Oncol. 2005;31(9):986–93.
47. Katz SC, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg. 2009;249(4):617–23.
48. Wang J, Xu LB, Liu C, Pang HW, Chen YJ, Ou QJ. Prognostic factors and outcome of 438 chinese patients with hepatocellular carcinoma underwent partial hepatectomy in a single center. World J Surg. 2010;34(10):2434–41.
49. Fan ST, Mau Lo C, Poon RT, Yeung C, Leung Liu C, Yuen WK, et al. Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. Ann Surg. 2011;253(4):745–58.
50. Kluger MD, Salceda JA, Laurent A, Tayar C, Duvoux C, Decaens T, et al. Liver resection for hepatocellular carcinoma in 313 western patients: tumor biology and underlying liver rather than tumor size drive prognosis. J Hepatol. 2015;62(5):1131–40.
51. Ng KK, Vauthey JN, Pawlik TM, Lauwers GY, Regimbeau JM, Belghiti J, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. Ann Surg Oncol. 2005;12(5):364–73.
52. Shindoh J, Andreou A, Aloia TA, Zimmitti G, Lauwers GY, Laurent A, et al. Microvascular invasion does not predict long-term survival in hepatocellular carcinoma up to 2 cm: reappraisal of the staging system for solitary tumors. Ann Surg Oncol. 2013;20(4):1223–9.
53. Pawlik TM, Poon RT, Abdalla EK, Ikai I, Nagorney DM, Belghiti J, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery. 2005;137(4):403–10.
54. Ikai I, Yamamoto Y, Yamamoto N, Terajima H, Hatano E, Shimahara Y, et al. Results of hepatic resection for hepatocellular carcinoma invading major portal and/or hepatic veins. Surg Oncol Clin N Am. 2003;12(1):65–75, ix.
55. Anonymous. Easl-eortc clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.
56. Yao FY, Hirose R, LaBerge JM, Davern TJ 3rd, Bass NM, Kerlan RK Jr, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl. 2005;11(12):1505–14.
57. Yamada R, Nakatsuka H, Nakamura K, Sato M, Itami M, Kobayashi N, et al. Hepatic artery embolization in 32 patients with unresectable hepatoma. Osaka City Med J. 1980;26(2):81–96.
58. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the precision v study. Cardiovasc Intervent Radiol. 2010;33(1):41–52.
59. Vogl TJ, Lammer J, Lencioni R, Malagari K, Watkinson A, Pilleul F, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with precision tace with drug-eluting beads: results from the precision v randomized trial. AJR Am J Roentgenol. 2011;197(4):W562–70.
60. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954;30(5):969–77.
61. Ridge JA, Bading JR, Gelbard AS, Benua RS, Daly JM. Perfusion of colorectal hepatic metastases. Relative distribution of flow from the hepatic artery and portal vein. Cancer. 1987;59(9):1547–53.
62. Lencioni R, Crocetti L, De Simone P, Filipponi F. Loco-regional interventional treatment of hepatocellular carcinoma: techniques, outcomes, and future prospects. Transpl Int. 2010;23(7):698–703.
63. Livraghi T, Bolondi L, Lazzaroni S, Marin G, Morabito A, Rapaccini GL, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. A study on 207 patients. Cancer. 1992;69(4):925–9.
64. Sala M, Llovet JM, Vilana R, Bianchi L, Sole M, Ayuso C, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology. 2004;40(6):1352–60.
65. Kuang M, Lu MD, Xie XY, Xu HX, Xu ZF, Liu GJ, et al. Ethanol ablation of hepatocellular carcinoma up to 5.0 cm by using a multipronged injection needle with high-dose strategy. Radiology. 2009;253(2):552–61.
66. Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology. 2005;129(1):122–30.
67. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut. 2005;54(8):1151–6.
68. Brunello F, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: a randomized controlled trial. Scand J Gastroenterol. 2008;43(6):727–35.
69. Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology. 2003;228(1):235–40.
70. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology. 2008;47(1):82–9.
71. Ahrar K, Matin S, Wood CG, Wallace MJ, Gupta S, Madoff DC, et al. Percutaneous radiofrequency ablation of renal tumors: technique, complications, and outcomes. J Vasc Interv Radiol. 2005;16(5):679–88.
72. Simon CJ, Dupuy DE, Mayo-Smith WW. Microwave ablation: principles and applications. Radiographics. 2005;25(Suppl 1):S69–83.
73. Lubner MG, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. J Vasc Interv Radiol. 2010;21(8 Suppl):S192–203.
74. Yu NC, Raman SS, Kim YJ, Lassman C, Chang X, Lu DS. Microwave liver ablation: influence of hepatic vein size on heat-sink effect in a porcine model. J Vasc Interv Radiol. 2008;19(7):1087–92.
75. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. Cryobiology. 1998;37(3):171–86.

76. Bageacu S, Kaczmarek D, Lacroix M, Dubois J, Forest J, Porcheron J. Cryosurgery for resectable and unresectable hepatic metastases from colorectal cancer. Eur J Surg Oncol. 2007;33(5):590–6.
77. Seifert JK, France MP, Zhao J, Bolton EJ, Finlay I, Junginger T, et al. Large volume hepatic freezing: association with significant release of the cytokines interleukin-6 and tumor necrosis factor a in a rat model. World J Surg. 2002;26(11):1333–41.
78. Sheen AJ, Poston GJ, Sherlock DJ. Cryotherapeutic ablation of liver tumours. Br J Surg. 2002;89(11):1396–401.
79. Wang W, Shi J, Xie WF. Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis. Liver Int. 2010;30(5):741–9.
80. Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G. Radiofrequency thermal ablation (rfa) after transarterial chemoembolization (tace) as a combined therapy for unresectable non-early hepatocellular carcinoma (hcc). Eur Radiol. 2006;16(3):661–9.
81. Rossi S, Garbagnati F, Lencioni R, Allgaier HP, Marchiano A, Fornari F, et al. Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. Radiology. 2000;217(1):119–26.
82. Yamasaki T, Kurokawa F, Shirahashi H, Kusano N, Hironaka K, Okita K. Percutaneous radiofrequency ablation therapy for patients with hepatocellular carcinoma during occlusion of hepatic blood flow. Comparison with standard percutaneous radiofrequency ablation therapy. Cancer. 2002;95(11):2353–60.
83. Lencioni R, Crocetti L, Petruzzi P, Vignali C, Bozzi E, Della Pina C, et al. Doxorubicin-eluting bead-enhanced radiofrequency ablation of hepatocellular carcinoma: a pilot clinical study. J Hepatol. 2008;49(2):217–22.
84. Gervais DA, Goldberg SN, Brown DB, Soulen MC, Millward SF, Rajan DK. Society of interventional radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. J Vasc Interv Radiol. 2009;20(1):3–8.
85. Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a markov model analysis. Hepatology. 2010;51(4):1284–90.
86. Lencioni R, Crocetti L. Local-regional treatment of hepatocellular carcinoma. Radiology. 2012;262(1):43–58.
87. Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: a meta-analysis. J Hepatol. 2010;52(3):380–8.
88. Bouza C, Lopez-Cuadrado T, Alcazar R, Saz-Parkinson Z, Amate JM. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterol. 2009;9:31.
89. Shibata T, Iimuro Y, Yamamoto Y, Maetani Y, Ametani F, Itoh K, et al. Small hepatocellular carcinoma: comparison of radiofrequency ablation and percutaneous microwave coagulation therapy. Radiology. 2002;223(2):331–7.
90. Morimoto M, Numata K, Kondo M, Moriya S, Morita S, Maeda S, et al. Radiofrequency ablation combined with transarterial chemoembolization for subcapsular hepatocellular carcinoma: a prospective cohort study. Eur J Radiol. 2013;82(3):497–503.
91. Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer. 2010;116(23):5452–60.
92. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37(2):429–42.
93. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxi A, Camma C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology. 2010;51(4):1274–83.
94. Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (tace) using drug eluting beads. Implications for clinical practice and trial design. J Hepatol. 2012;56(6):1330–5.
95. Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, et al. Yttrium(90) radioembolization for intermediate-advanced hepatocarcinoma: a phase ii study. Hepatology. 2013;57(5):1826–37.
96. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across barcelona clinic liver cancer stages: a european evaluation. Hepatology. 2011;54(3):868–78.
97. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.
98. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the asia-pacific region with advanced hepatocellular carcinoma: a phase iii randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25–34.
99. Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, et al. Phase ii study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2006;24(26):4293–300.
100. Park JW, Koh YH, Kim HB, Kim HY, An S, Choi JI, et al. Phase ii study of concurrent transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma. J Hepatol. 2012;56(6):1336–42.
101. Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. Phase ii trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol. 2011;29(30):3960–7.
102. Austin-Seymour MM, Chen GT, Castro JR, Saunders WM, Pitluck S, Woodruff KH, et al. Dose volume histogram analysis of liver radiation tolerance. Int J Radiat Oncol Biol Phys. 1986;12(1):31–5.
103. Lawrence TS, Ten Haken RK, Kessler ML, Robertson JM, Lyman JT, Lavigne ML, et al. The use of 3-d dose volume analysis to predict radiation hepatitis. Int J Radiat Oncol Biol Phys. 1992;23(4):781–8.
104. Dawson LA, Ten Haken RK. Partial volume tolerance of the liver to radiation. Semin Radiat Oncol. 2005;15(4):279–83.
105. Dawson LA, McGinn CJ, Normolle D, Ten Haken RK, Walker S, Ensminger W, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol. 2000;18(11):2210–8.
106. Wurm RE, Gum F, Erbel S, Schlenger L, Scheffler D, Agaoglu D, et al. Image guided respiratory gated hypofractionated stereotactic body radiation therapy (h-sbrt) for liver and lung tumors: initial experience. Acta Oncol. 2006;45(7):881–9.
107. Brock KK, Dawson LA. Adaptive management of liver cancer radiotherapy. Semin Radiat Oncol. 2010;20(2):107–15.
108. Verellen D, Depuydt T, Gevaert T, Linthout N, Tournel K, Duchateau M, et al. Gating and tracking, 4d in thoracic tumours. Cancer Radiotherapie: journal de la Societe francaise de radiotherapie oncologique. 2010;14(6–7):446–54.
109. Iizuka Y, Matsuo Y, Ishihara Y, Akimoto M, Tanabe H, Takayama K, et al. Dynamic tumor-tracking radiotherapy with real-time monitoring for liver tumors using a gimbal mounted linac. Radiother Oncol. 2015;117(3):496–500.
110. Eccles C, Brock KK, Bissonnette JP, Hawkins M, Dawson LA. Reproducibility of liver position using active breathing coor-

dinator for liver cancer radiotherapy. Int J Radiat Oncol Biol Phys. 2006;64(3):751–9.
111. Dawson LA, Brock KK, Kazanjian S, Fitch D, McGinn CJ, Lawrence TS, et al. The reproducibility of organ position using active breathing control (abc) during liver radiotherapy. Int J Radiat Oncol Biol Phys. 2001;51(5):1410–21.
112. Tina Marie B, Sam B, Peter B, Ravi M, Sanjay G, Christopher N, et al. Respiratory gating with epid-based verification: the mdacc experience. Phys Med Biol. 2009;54(11):3379.
113. Heinzerling JH, Anderson JF, Papiez L, Boike T, Chien S, Zhang G, et al. Four-dimensional computed tomography scan analysis of tumor and organ motion at varying levels of abdominal compression during stereotactic treatment of lung and liver. Int J Radiat Oncol Biol Phys. 2008;70(5):1571–8.
114. Lovelock DM, Zatcky J, Goodman K, Yamada Y. The effectiveness of a pneumatic compression belt in reducing respiratory motion of abdominal tumors in patients undergoing stereotactic body radiotherapy. Technol Cancer Res Treat. 2014;13(3):259–67.
115. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase ii study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol. 2006;24(30):4833–9.
116. Dawson LA, Eccles C, Craig T. Individualized image guided iso-ntcp based liver cancer sbrt. Acta Oncol. 2006;45(7):856–64.
117. Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, et al. Phase i study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2008;26(4):657–64.
118. Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RKS, et al. Sequential phase i and ii trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013;31(13):1631–9.
119. Wang X, Krishnan S, Zhang X, Dong L, Briere T, Crane CH, et al. Proton radiotherapy for liver tumors: dosimetric advantages over photon plans. Med Dosim. 2008;33(4):259–67.
120. Petersen JB, Lassen Y, Hansen AT, Muren LP, Grau C, Hoyer M. Normal liver tissue sparing by intensity-modulated proton stereotactic body radiotherapy for solitary liver tumours. Acta Oncol. 2011;50(6):823–8.
121. Fukumitsu N, Sugahara S, Nakayama H, Fukuda K, Mizumoto M, Abei M, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2009;74(3):831–6.
122. Kawashima M, Furuse J, Nishio T, Konishi M, Ishii H, Kinoshita T, et al. Phase ii study of radiotherapy employing proton beam for hepatocellular carcinoma. J Clin Oncol. 2005;23(9):1839–46.
123. Mizumoto M, Okumura T, Hashimoto T, Fukuda K, Oshiro Y, Fukumitsu N, et al. Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. Int J Radiat Oncol Biol Phys. 2011;81(4):1039–45.
124. Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, Kaseb AO, Bishop AJ, Swanick CW, Koay EJ, Thames HD. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma. J Clin Oncol. 2016;34(3):219.
125. Crane C, Koay EJ. Solutions that enable ablative radiotherapy for large liver tumors: fractionated dose painting, simultaneous integrated protection, motion management, and computed tomography image guidance. Cancer. 2016;122(13):1974–86.
126. Seong J, Koom WS, Park HC. Radiotherapy for painful bone metastases from hepatocellular carcinoma. Liver Int. 2005;25(2):261–5.
127. Kaizu T, Karasawa K, Tanaka Y, Matuda T, Kurosaki H, Tanaka S, et al. Radiotherapy for osseous metastases from hepatocellular carcinoma: a retrospective study of 57 patients. Am J Gastroenterol. 1998;93(11):2167–71.
128. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma: from palliation to cure. Cancer. 2006;106(8):1653–63.
129. Jiang W, Zeng ZC, Zhang JY, Fan J, Zeng MS, Zhou J. Palliative radiation therapy for pulmonary metastases from hepatocellular carcinoma. Clin Exp Metastasis. 2012;29(3):197–205.
130. Toya R, Murakami R, Baba Y, Nishimura R, Morishita S, Ikeda O, et al. Conformal radiation therapy for portal vein tumor thrombosis of hepatocellular carcinoma. Radiother Oncol. 2007;84(3):266–71.
131. Tazawa J, Maeda M, Sakai Y, Yamane M, Ohbayashi H, Kakinuma S, et al. Radiation therapy in combination with transcatheter arterial chemoembolization for hepatocellular carcinoma with extensive portal vein involvement. J Gastroenterol Hepatol. 2001;16(6):660–5.
132. Gayou O, Day E, Mohammadi S, Kirichenko A. A method for registration of single photon emission computed tomography (spect) and computed tomography (ct) images for liver stereotactic radiotherapy (srt). Med Phys. 2012;39(12):7398–401.
133. Hoefs JC, Wang F, Kanel G. Functional measurement of nonfibrotic hepatic mass in cirrhotic patients. Am J Gastroenterol. 1997;92(11):2054–8.
134. Wisse E, Braet F, Luo D, De Zanger R, Jans D, Crabbe E, et al. Structure and function of sinusoidal lining cells in the liver. Toxicol Pathol. 1996;24(1):100–11.
135. Kirichenko A, Gayou O, Day E, Lappinen E, Thai N, Parda D. Stereotactic radiotherapy (srt) for hepatocellular carcinoma (hcc) with 3-d ct and single photon emission computed tomography (ct/spect) functional treatment planning. Int J Radiat Oncol Biol Phys. 2014; In review.
136. Nowak AK, Chow PK, Findlay M. Systemic therapy for advanced hepatocellular carcinoma: a review. Eur J Cancer. 2004;40(10):1474–84.
137. Palmer DH, Hussain SA, Johnson PJ. Systemic therapies for hepatocellular carcinoma. Expert Opin Investig Drugs. 2004;13(12):1555–68.
138. Thomas MB, Morris JS, Chadha R, Iwasaki M, Kaur H, Lin E, et al. Phase ii trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. J Clin Oncol. 2009;27(6):843–50.
139. Olweny CL, Toya T, Katongole-Mbidde E, Mugerwa J, Kyalwazi SK, Cohen H. Treatment of hepatocellular carcinoma with adriamycin. Preliminary communication. Cancer. 1975;36(4):1250–7.
140. Falkson G, Moertel CG, Lavin P, Pretorius FJ, Carbone PP. Chemotherapy studies in primary liver cancer: a prospective randomized clinical trial. Cancer. 1978;42(5):2149–56.
141. Tetef M, Doroshow J, Akman S, Coluzzi P, Leong L, Margolin K, et al. 5-fluorouracil and high-dose calcium leucovorin for hepatocellular carcinoma: a phase ii trial. Cancer Investig. 1995;13(5):460–3.
142. Link JS, Bateman JR, Paroly WS, Durkin WJ, Peters RL. 5-flourouracil in hepatocellular carcinoma: report of twenty-one cases. Cancer. 1977;39(5):1936–9.
143. Porta C, Moroni M, Nastasi G, Arcangeli G. 5-fluorouracil and d,l-leucovorin calcium are active to treat unresectable hepatocellular carcinoma patients: preliminary results of a phase ii study. Oncology. 1995;52(6):487–91.
144. Chambers CA, Sullivan TJ, Allison JP. Lymphoproliferation in ctla-4-deficient mice is mediated by costimulation-dependent activation of cd4+ t cells. Immunity. 1997;7(6):885–95.
145. Friedman MA. Primary hepatocellular cancer--present results and future prospects. Int J Radiat Oncol Biol Phys. 1983;9(12):1841–50.
146. Walko CM, Lindley C. Capecitabine: a review. Clin Ther. 2005;27(1):23–44.
147. Xia Y, Qiu Y, Li J, Shi L, Wang K, Xi T, et al. Adjuvant therapy with capecitabine postpones recurrence of hepatocellular

carcinoma after curative resection: a randomized controlled trial. Ann Surg Oncol. 2010;17(12):3137–44.
148. Fuchs CS, Clark JW, Ryan DP, Kulke MH, Kim H, Earle CC, et al. A phase ii trial of gemcitabine in patients with advanced hepatocellular carcinoma. Cancer. 2002;94(12):3186–91.
149. Kubicka S, Rudolph KL, Tietze MK, Lorenz M, Manns M. Phase ii study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. Hepato-Gastroenterology. 2001;48(39):783–9.
150. Yang TS, Lin YC, Chen JS, Wang HM, Wang CH. Phase ii study of gemcitabine in patients with advanced hepatocellular carcinoma. Cancer. 2000;89(4):750–6.
151. Boige V, Taieb J, Hebbar M, Malka D, Debaere T, Hannoun L, et al. Irinotecan as first-line chemotherapy in patients with advanced hepatocellular carcinoma: a multicenter phase ii study with dose adjustment according to baseline serum bilirubin level. Eur J Cancer. 2006;42(4):456–9.
152. Hsu C, Chen CN, Chen LT, Wu CY, Yang PM, Lai MY, et al. Low-dose thalidomide treatment for advanced hepatocellular carcinoma. Oncology. 2003;65(3):242–9.
153. Chao Y, Chan WK, Birkhofer MJ, Hu OY, Wang SS, Huang YS, et al. Phase ii and pharmacokinetic study of paclitaxel therapy for unresectable hepatocellular carcinoma patients. Br J Cancer. 1998;78(1):34–9.
154. Lin HL, Liu TY, Chau GY, Lui WY, Chi CW. Comparison of 2-methoxyestradiol-induced, docetaxel-induced, and paclitaxel-induced apoptosis in hepatoma cells and its correlation with reactive oxygen species. Cancer. 2000;89(5):983–94.
155. Okada S, Okazaki N, Nose H, Shimada Y, Yoshimori M, Aoki K. A phase 2 study of cisplatin in patients with hepatocellular carcinoma. Oncology. 1993;50(1):22–6.
156. Morstyn G, Ihde DC, Eddy JL, Bunn PA, Cohen MH, Minna JD. Combination chemotherapy of hepatocellular carcinoma with doxorubicin and streptozotocin. Am J Clin Oncol. 1983;6(5):547–51.
157. Chlebowski RT, Chan KK, Tong MJ, Weiner JM, Ryden VM, Bateman JR. Adriamycin and methyl-ccnu combination therapy in hepatocellular carcinoma: clinical and pharmacokinetic aspects. Cancer. 1981;48(5):1088–95.
158. Falkson CI, Falkson G. A phase ii evaluation of clofazimine plus doxorubicin in advanced, unresectable primary hepatocellular carcinoma. Oncology. 1999;57(3):232–5.
159. Yang TS, Wang CH, Hsieh RK, Chen JS, Fung MC. Gemcitabine and doxorubicin for the treatment of patients with advanced hepatocellular carcinoma: a phase i-ii trial. Ann Oncol. 2002;13(11):1771–8.
160. Ellis PA, Norman A, Hill A, O'Brien ME, Nicolson M, Hickish T, et al. Epirubicin, cisplatin and infusional 5-fluorouracil (5-fu) (ecf) in hepatobiliary tumours. Eur J Cancer. 1995;31A(10):1594–8.
161. Boucher E, Corbinais S, Brissot P, Boudjema K, Raoul JL. Treatment of hepatocellular carcinoma (hcc) with systemic chemotherapy combining epirubicin, cisplatinum and infusional 5-fluorouracil (ecf regimen). Cancer Chemother Pharmacol. 2002;50(4):305–8.
162. Leung TW, Tang AM, Zee B, Yu SC, Lai PB, Lau WY, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer. 2002;94(2):421–7.
163. Kajanti MJ, Pyrhonen SO. Phase ii intravenous study of epirubicin with 5-fluorouracil in patients with advanced hepatocellular carcinoma. Eur J Cancer. 1991;27(12):1620–2.
164. Al-Idrissi HY, Ibrahim EM, Abdel Satir A, Satti MB, Al-Kasem S, Al-Qurain A. Primary hepatocellular carcinoma in the eastern province of saudi arabia: treatment with combination chemotherapy using 5-fluorouracil, adriamycin and mitomycin-c. Hepato-Gastroenterology. 1985;32(1):8–10.
165. Shim JH, Park JW, Nam BH, Lee WJ, Kim CM. Efficacy of combination chemotherapy with capecitabine plus cisplatin in patients with unresectable hepatocellular carcinoma. Cancer Chemother Pharmacol. 2009;63(3):459–67.
166. Lee JO, Lee KW, Oh DY, Kim JH, Im SA, Kim TY, et al. Combination chemotherapy with capecitabine and cisplatin for patients with metastatic hepatocellular carcinoma. Ann Oncol. 2009;20(8):1402–7.
167. Lombardi G, Zustovich F, Farinati F, Cillo U, Vitale A, Zanus G, et al. Pegylated liposomal doxorubicin and gemcitabine in patients with advanced hepatocellular carcinoma: results of a phase 2 study. Cancer. 2011;117(1):125–33.
168. Louafi S, Boige V, Ducreux M, Bonyhay L, Mansourbakht T, de Baere T, et al. Gemcitabine plus oxaliplatin (gemox) in patients with advanced hepatocellular carcinoma (hcc): results of a phase ii study. Cancer. 2007;109(7):1384–90.
169. Qin S, Cheng Y, Liang J, Shen L, Bai Y, Li J, et al. Efficacy and safety of the folfox4 regimen versus doxorubicin in chinese patients with advanced hepatocellular carcinoma: a subgroup analysis of the each study. Oncologist. 2014;19(11):1169–78.
170. Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, et al. A randomized phase iii study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (piaf) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst. 2005;97(20):1532–8.
171. Kaseb AO, Shindoh J, Patt YZ, Roses RE, Zimmitti G, Lozano RD, et al. Modified cisplatin/interferon alpha-2b/doxorubicin/5-fluorouracil (piaf) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma. Cancer. 2013;119(18):3334–42.
172. Huang CC, Wu MC, Xu GW, Li DZ, Cheng H, Tu ZX, et al. Overexpression of the mdr1 gene and p-glycoprotein in human hepatocellular carcinoma. J Natl Cancer Inst. 1992;84(4):262–4.
173. Semela D, Dufour JF. Angiogenesis and hepatocellular carcinoma. J Hepatol. 2004;41(5):864–80.
174. O'Neil BH, Goff LW, Kauh JS, Strosberg JR, Bekaii-Saab TS, Lee RM, et al. Phase ii study of the mitogen-activated protein kinase 1/2 inhibitor selumetinib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2011;29(17):2350–6.
175. Lee J, Park JO, Kim WS, Park SH, Park KW, Choi MS, et al. Phase ii study of doxorubicin and cisplatin in patients with metastatic hepatocellular carcinoma. Cancer Chemother Pharmacol. 2004;54(5):385–90.
176. Parikh PM, Fuloria J, Babu G, Doval DC, Awasthy BS, Pai VR, et al. A phase ii study of gemcitabine and cisplatin in patients with advanced hepatocellular carcinoma. Trop Gastroenterol. 2005;26(3):115–8.
177. Zaanan A, Williet N, Hebbar M, Dabakuyo TS, Fartoux L, Mansourbakht T, et al. Gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma: a large multicenter ageo study. J Hepatol. 2013;58(1):81–8.
178. Leung TW, Patt YZ, Lau WY, Ho SK, Yu SC, Chan AT, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res. 1999;5(7):1676–81.
179. Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. JAMA. 2010;304(19):2154–60.
180. Siegel AB, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, et al. Phase ii trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. J Clin Oncol. 2008;26(18):2992–8.

181. Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase iii trial. J Clin Oncol. 2013;31(32):4067–75.
182. McNamara MG, Le LW, Horgan AM, Aspinall A, Burak KW, Dhani N, et al. A phase ii trial of second-line axitinib following prior antiangiogenic therapy in advanced hepatocellular carcinoma. Cancer. 2015;121(10):1620–7.
183. Zhu AX, Rosmorduc O, Evans TR, Ross PJ, Santoro A, Carrilho FJ, et al. Search: a phase iii, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2015;33(6):559–66.
184. Kaseb AO, Garrett-Mayer E, Morris JS, Xiao L, Lin E, Onicescu G, et al. Efficacy of bevacizumab plus erlotinib for advanced hepatocellular carcinoma and predictors of outcome: final results of a phase ii trial. Oncology. 2012;82(2):67–74.
185. Kaseb AO, Morris JS, Iwasaki M, Al-Shamsi HO, Raghav KP, Girard L, et al. Phase ii trial of bevacizumab and erlotinib as a second-line therapy for advanced hepatocellular carcinoma. Onco Targets Ther. 2016;9:773–80.
186. Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase iii brisk-fl study. J Clin Oncol. 2013;31(28):3517–24.
187. Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase iii brisk-ps study. J Clin Oncol. 2013;31(28):3509–16.
188. Zhu AX, Kudo M, Assenat E, Cattan S, Kang YK, Lim HY, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the evolve-1 randomized clinical trial. JAMA. 2014;312(1):57–67.
189. Santoro A, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol. 2013;14(1):55–63.
190. El-Khoueiry A, Melero I, Crocenzi T, Welling T, Yau TC, Yeo W, et al. Phase i/ii safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (hcc): Ca209-040. J Clin Oncol. 2015;33(suppl; abstr):LBA101.
191. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase iii trial. J Hepatol. 2012;57(4):821–9.
192. Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schutz G, et al. Regorafenib (bay 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1):245–55.
193. Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (reach): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015;16(7):859–70.
194. Abou-Alfa G, Qin S, Ryoo B, editors. Phase iii randomized study of second line adi-peg 20 (a) plus best supportive care versus placebo (p) plus best supportive care in patients (pts) with advanced hepatocellular carcinoma (hcc). Proc Am Soc Clin Oncol; 2016.
195. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (resorce): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56–66.
196. Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. Ann Oncol. 2008;19(9):1613–8.
197. Faivre S, Raymond E, Boucher E, Douillard J, Lim HY, Kim JS, et al. Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase ii study. Lancet Oncol. 2009;10(8):794–800.
198. Zhu AX, Sahani DV, Duda DG, di Tomaso E, Ancukiewicz M, Catalano OA, et al. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase ii study. J Clin Oncol. 2009;27(18):3027–35.
199. Boige V, Malka D, Bourredjem A, Dromain C, Baey C, Jacques N, et al. Efficacy, safety, and biomarkers of single-agent bevacizumab therapy in patients with advanced hepatocellular carcinoma. Oncologist. 2012;17(8):1063–72.
200. Govindarajan R, Siegel E, Makhoul I, Williamson S. Bevacizumab and erlotinib in previously untreated inoperable and metastatic hepatocellular carcinoma. Am J Clin Oncol. 2013;36(3):254–7.
201. Yau T, Wong H, Chan P, Yao TJ, Pang R, Cheung TT, et al. Phase ii study of bevacizumab and erlotinib in the treatment of advanced hepatocellular carcinoma patients with sorafenib-refractory disease. Investig New Drugs. 2012;30(6):2384–90.
202. Philip PA, Mahoney MR, Holen KD, Northfelt DW, Pitot HC, Picus J, et al. Phase 2 study of bevacizumab plus erlotinib in patients with advanced hepatocellular cancer. Cancer. 2012;118(9):2424–30.
203. Zhu AX, Blaszkowsky LS, Ryan DP, Clark JW, Muzikansky A, Horgan K, et al. Phase ii study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2006;24(12):1898–903.
204. Hsu CH, Yang TS, Hsu C, Toh HC, Epstein RJ, Hsiao LT, et al. Efficacy and tolerability of bevacizumab plus capecitabine as first-line therapy in patients with advanced hepatocellular carcinoma. Br J Cancer. 2010;102(6):981–6.
205. Sun W, Sohal D, Haller DG, Mykulowycz K, Rosen M, Soulen MC, et al. Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. Cancer. 2011;117(14):3187–92.
206. Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. Drugs R&D. 2011;11(2):113–26.
207. Hu-Lowe DD, Zou HY, Grazzini ML, Hallin ME, Wickman GR, Amundson K, et al. Nonclinical antiangiogenesis and antitumor activities of axitinib (ag-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res. 2008;14(22):7272–83.
208. Ayers M, Fargnoli J, Lewin A, Wu Q, Platero JS. Discovery and validation of biomarkers that respond to treatment with brivanib alaninate, a small-molecule vegfr-2/fgfr-1 antagonist. Cancer Res. 2007;67(14):6899–906.
209. Cai ZW, Zhang Y, Borzilleri RM, Qian L, Barbosa S, Wei D, et al. Discovery of brivanib alaninate ((s)-((r)-1-(4-(4-fluoro-2-methyl-1h-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4] triazin-6-yloxy) propan-2-yl)2-aminopropanoate), a novel prodrug of dual vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinase inhibitor (bms-540215). J Med Chem. 2008;51(6):1976–80.
210. Park JW, Finn RS, Kim JS, Karwal M, Li RK, Ismail F, et al. Phase ii, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res. 2011;17(7):1973–83.
211. Hay N, Sonenberg N. Upstream and downstream of mtor. Genes Dev. 2004;18(16):1926–45.
212. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated b7-h1 promotes t-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002;8(8):793–800.

213. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-h1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their pd-1 expression. Clin Cancer Res. 2004;10(15):5094–100.
214. Brown JA, Dorfman DM, Ma FR, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances t cell activation and cytokine production. J Immunol. 2003;170(3):1257–66.
215. Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of pd-l1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res. 2009;15(3):971–9.
216. Sangro B, Gomez-Martin C, de la Mata M, Inarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of ctla-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis c. J Hepatol. 2013;59(1):81–8.
217. Kuang DM, Zhao Q, Peng C, Xu J, Zhang JP, Wu C, et al. Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through pd-l1. J Exp Med. 2009;206(6):1327–37.
218. Andarini S, Kikuchi T, Nukiwa M, Pradono P, Suzuki T, Ohkouchi S, et al. Adenovirus vector-mediated in vivo gene transfer of ox40 ligand to tumor cells enhances antitumor immunity of tumor-bearing hosts. Cancer Res. 2004;64(9):3281–7.
219. Ishii N, Takahashi T, Soroosh P, Sugamura K. Ox40-ox40 ligand interaction in t-cell-mediated immunity and immunopathology. Adv Immunol. 2010;105:63–98.
220. Weinberg AD, Morris NP, Kovacsovics-Bankowski M, Urba WJ, Curti BD. Science gone translational: the ox40 agonist story. Immunol Rev. 2011;244(1):218–31.
221. Croft M. Control of immunity by the tnfr-related molecule ox40 (cd134). Annu Rev Immunol. 2010;28:57–78.
222. Zaini J, Andarini S, Tahara M, Saijo Y, Ishii N, Kawakami K, et al. Ox40 ligand expressed by dcs costimulates nkt and cd4+ th cell antitumor immunity in mice. J Clin Invest. 2007;117(11):3330–8.
223. Kjaergaard J, Tanaka J, Kim JA, Rothchild K, Weinberg A, Shu S. Therapeutic efficacy of ox-40 receptor antibody depends on tumor immunogenicity and anatomic site of tumor growth. Cancer Res. 2000;60(19):5514–21.
224. Piconese S, Valzasina B, Colombo MP. Ox40 triggering blocks suppression by regulatory t cells and facilitates tumor rejection. J Exp Med. 2008;205(4):825–39.
225. Sangro B, Melero I, Yau T, Hsu C, Kudo M, Crocenzi T, et al. Safety and antitumor activity of nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (hcc): interim analysis of dose-expansion cohorts from the phase 1/2 checkmate-040 study. Liver Cancer. 2016.
226. Scagliotti GV, Novello S, von Pawel J. The emerging role of met/hgf inhibitors in oncology. Cancer Treat Rev. 2013;39(7):793–801.
227. Xiang QF, Zhang DM, Wang JN, Zhang HW, Zheng ZY, Yu DC, et al. Cabozantinib reverses multidrug resistance of human hepatoma hepg2/adr cells by modulating the function of p-glycoprotein. Liver Int. 2015;35(3):1010–23.
228. Prior IA, Lewis PD, Mattos C. A comprehensive survey of ras mutations in cancer. Cancer Res. 2012;72(10):2457–67.
229. Schmidt CM, McKillop IH, Cahill PA, Sitzmann JV. Increased mapk expression and activity in primary human hepatocellular carcinoma. Biochem Biophys Res Commun. 1997;236(1):54–8.
230. Ito Y, Sasaki Y, Horimoto M, Wada S, Tanaka Y, Kasahara A, et al. Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma. Hepatology. 1998;27(4):951–8.
231. Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (adore): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol. [Clinical Trial, Phase II Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non--U.S. Gov't]. 2014;15(11):1245–53.

Resectable and Borderline Resectable Pancreatic Cancer

14

Megan A. Stevenson, Sameer H. Patel, and Syed A. Ahmad

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a devastating illness that takes the lives of virtually all diagnosed. It is the fourth-leading cause of cancer-related death in the United States, and the overall 5-year survival is 8.2% [1]. Surgical resection remains the only opportunity for cure, but a staggering 80–85% of patients present with locally advanced or metastatic disease and are not surgical candidates. What is perhaps more telling is that of the 15–20% of patients with resectable pancreas cancer who are eligible for an operation with curative intent, the majority will then go on to develop local, regional, and/or systemic recurrences, and their 5-year survival is less than 20% [2, 3].

Disappointing overall survival in surgically resected patients has prompted the search for adjuncts in the treatment of PDAC. Considerable effort has been devoted to the development of effective adjuvant and neoadjuvant therapies, as well as more sensitive and specific imaging and screening modalities to aid in earlier diagnosis and disease staging. As surgical resection remains central to disease eradication, the importance of a complete or R0 resection has been established in terms of its benefit on overall survival. Hence, the determination of resectability is paramount. Improved diagnostics and advancements in surgical techniques have led to the emergence of borderline resectable tumors—a spectrum of disease falling between overtly resectable and locally advanced, unresectable PDACs. Uniformly defining this patient population is essential, both to optimally care for more patients, and for the development of stage-specific, novel clinical trials. A multimodal approach to patient care done in high-volume centers ensures that physicians with the most expertise will be routinely treating this complex patient population. Further advancements in the diagnostics and therapeutics of patients with pancreas cancer will require collaboration of experts across centers.

M. A. Stevenson · S. H. Patel
Department of Surgery, Division of Surgical Oncology, University of Cincinnati Medical Center, Cincinnati, OH, USA

S. A. Ahmad (✉)
Department of Surgery, Division of Surgical Oncology, Pancreas Disease Center, University of Cincinnati Cancer Institute, University of Cincinnati Medical Center, Cincinnati, OH, USA
e-mail: syed.ahmad@uc.edu

Definitions: Resectable and Borderline Resectable Pancreas Cancer

Resectable PDAC has been defined by the National Comprehensive Cancer Network (NCCN) and subsequently by Callery et al. [4, 5] as (1) no distant metastases (i.e., no extrapancreatic disease); (2) no radiographic evidence of superior mesenteric vein (SMV) and portal vein (PV) abutment, distortion, tumor thrombus, or venous encasement; and (3) clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA). These patients are offered operation with curative intent if, upon history and physical exam, they are deemed fit for surgery. At the other end of the spectrum are unresectable tumors. They can be locally advanced unresectable, with arterial encasement (celiac axis, SMA, or both), and/or venous occlusion (SMV, PV, or SMV-PV confluence), or they can be metastatic to distant sites. Well-localized tumors not impinging upon the vasculature are easy to classify as resectable, just as tumors with distant metastasis are easy to classify as unresectable. The gray area comes when tumors begin to "abut" or "encase" the mesenteric vasculature, as the percentage of vascular encasement has been shown to help predict resectability [6] and also lead to more technically demanding operations that often require a surgeon experienced in vascular resection and reconstruction. Furthermore, as discussed previously, the precise degree of vascular involvement is subject to interpretation by surgeons and radiologists, and this leads to variation among centers in accurately defining the resectable patient population.

Borderline resectable pancreas cancer has emerged as an area of interest in defining patients who may be eligible for

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_14

resection but are high risk for positive pathologic margins that would adversely impact survival. This patient population has tumors with varying degrees of mesenteric vascular involvement, and many of these patients have traditionally not been offered surgery due to both concerns for unresectability and for the technical demands brought on by vascular involvement. However, patients falling in this gray area are of interest, because in the right setting, the potential for an R0 resection often exists. At centers with experienced pancreas surgeons skilled in techniques of vascular resection and reconstruction, several groups have shown these operations not only to be feasible and safe, but also to yield equivalent survival as for patients with straightforward resectable disease [7, 8], as long as an R0 resection is achieved. Overall survival for these patients is additionally superior to patients with locally advanced disease who undergo nonoperative management [9, 10]. These findings are encouraging and emphasize the importance of accurately defining this "borderline" population, in order to stage them appropriately.

Over the years, many groups have attempted to objectively define the tumor-vascular interface. Ishikawa et al. first detailed tumor involvement at the SMV-PV confluence in 1992 when they retrospectively reviewed the portal phase of SMA angiography on 50 patients [11]. They then classified their findings into five types: (I) normal confluence, (II) smooth shift without narrowing, (III) unilateral narrowing, (IV) bilateral narrowing, and (V) bilateral narrowing and the presence of collateral veins. They noted that resected patients with extensive venous involvement (types IV and V) had a poorer prognosis than unresectable patients, illustrating again that increasing vascular involvement is a predictor of positive pathologic margins. The Ishikawa vein deformity is still commonly referred to in the literature.

In 1995, investigators out of MD Anderson Cancer Center (MDACC) categorized the extent of tumor-vascular involvement on preoperative computed tomography (CT) scan of 56 patients with PDAC into six types: A through F [12]. They then correlated these preoperative findings with the actual tumor-vascular relationship found in the operating room. In type A and B involvement, where there was a fat plane and normal pancreatic parenchyma, respectively, separating the tumor from adjacent vasculature, the patients were resectable in 21 of 22 cases (95%). Types E and F, on the other end of the spectrum, were tumors that completely encircled or occluded the vessel, respectively. None of those patients were able to undergo R0 resection. In the middle were types C and D. Type C tumors on imaging were inseparable from the vasculature, but the point of contact formed a convexity against the vessel, and type D tumors partially encircled the vasculature. Not surprisingly, resectability rate decreased with increasing vascular involvement. Shortly thereafter, Lu et al. [13] proposed an alternative grading system in which a 0–4 scale was assigned based on the circumferential contiguity of tumor to vessel. Grade 0 were tumors without contiguity to vessel wall. Grade 1 tumors were contiguous with less than one-quarter of the vessel wall circumference, grade 2 from over one-quarter to one-half of the vessel circumference, grade 3 one-half to three-quarters, and grade 4 greater than three-quarters contiguity or vessel constriction. Although the study size was small, there was no distinction between arterial and venous involvement, and the surgeons were not blinded to the preoperative findings of the radiologists; the authors found tumor involvement of more than one-half of a surrounding vessel to be highly predictive of unresectability. More recently in 2014, Tran Cao et al. [14] identified all patients who had undergone pancreaticoduodenectomy at MDACC over an 8-year period and re-reviewed their preoperative imaging to assess the degree of tumor-vein circumferential interface (TVI). TVI was defined as having either no interface, ≤180° of vessel circumference, >180° of vessel circumference, or vascular occlusion, and findings were then correlated with the subsequent need for venous resection, histologic venous invasion, and overall survival. A total of 254 patients were included for analysis, 98 of whom (38.5%) required SMV-PV resection. The authors concluded that a TVI > 180° was accurately predictive ($p < 0.001$) of the need for venous resection, as 89.5% of patients with either this interface ($n = 25$ of 28 patients) or occlusion ($n = 9$ of 10 patients) required vascular resection. Histologic invasion of the vein was seen in 82.4% of patients with TVI > 180° or occlusion. Additionally, overall survival was improved in patients with TVI ≤ 180°.

These studies provided a framework for defining the relationship between TVI, resectability, and survival. The NCCN provided the first published definition of borderline resectable tumors in 2004 [15]. Their definition described borderline tumors as those that abutted the SMA and had severe one-sided SMV or PV impingement, gastroduodenal artery (GDA) encasement up to the hepatic artery, or colon/mesocolon invasion. In 2006, the MD Anderson Cancer Center Pancreas Center Group more precisely defined borderline resectable tumors as having tumor abutment ≤180° of the SMA or celiac axis circumference, a short-segment abutment or encasement of the common hepatic artery (CHA) (most commonly at the GDA origin), or segmental venous occlusion amenable to venous reconstruction (requiring adequate SMV below and PV above the occlusion) [16]. They further clarified that *abutment* or *involvement* represented ≤180° vessel circumference, whereas *encasement* represented ≥180° of vessel circumference. In 2008, Katz et al. expanded their MDACC definition of borderline resectability by subdividing patients into types A, B, or C [17]. Type A patients were consistent with their 2006 definition, whereas type B patients had questionable extrapancreatic metastatic disease, and type C were patients with marginal performance status. These latter two categories were felt to be important because they relied on the clinical judgment of a multidisci-

plinary team when being considered for surgery. Axial imaging with questionable occult metastatic disease necessitates a radiologist experienced in pancreas imaging. Exploratory laparotomy and pancreatectomy even without vascular reconstruction is a major abdominal operation, and the patient's ability to tolerate this procedure must be confirmed preoperatively. At MD Anderson, a large center with a broad referral base, increasing numbers of these type "B" and "C" patients are being evaluated for treatment, and the center has stressed the importance of accurately staging these patients in order to better administer stage-specific treatment, minimize treatment indecision, and avoid unindicated operations in patients with metastatic disease [17].

In 2009, Callery et al. authored a consensus statement by the American Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, and the Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT), on borderline resectable pancreas cancer, which has subsequently been endorsed by the NCCN [4]. These tumors (1) have no distant metastases; (2) have venous involvement of the SMV/PV demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/PV but without encasement of the nearby arteries, or short-segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction; (3) have GDA encasement up to the hepatic artery with either short-segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis; or (4) have tumor abutment of the SMA not exceeding >180° of the circumference of the vessel wall.

The above definitions from MDACC and AHPBA/SSO/SSAT are similar in their description of arterial involvement but differ in their description of what constitutes borderline resectable disease with regard to venous involvement. The AHPBA/SSO/SSAT consensus categorizes *any* degree of venous involvement as being borderline resectable, and authors at MDACC have raised concerns that this definition may be somewhat broad [18], because it has the potential to incorporate patients who may in fact be resectable upfront. In fact, as Kelly et al. have noted, the multiple proposed definitions of borderline resectable disease vary primarily on their criteria for venous involvement, and no single definition exists [19].

More recently, in an effort to standardize across institutions the definition of borderline resectable PDAC, the Intergroup Trial published in 2013 a collaborative and objective definition of borderline resectable PDAC that included cancers with one or more of the following: (1) an interface between the primary tumor and SMV-PV measuring 180° or greater of the circumference of the vein wall, and/or (2) short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction, and/or (3) short-segment interface (of any degree) between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction, and/or (4) an interface between the tumor and SMA or celiac trunk measuring less than 180° of the circumference of the artery wall [20]. This definition has subsequently been endorsed by the NCCN and is the foundation upon which current multi-institutional clinical trials of multimodal therapy for patients with borderline resectable PDAC are being designed. Summary of NCCN definitions of resectable, borderline, and unresectable is seen in Table 14.1 [15] and examples in Fig 14.1a–c.

Table 14.1 Definition of resectable, borderline, and unresectable pancreas adenocarcinoma [15]

Resectable	Borderline	Unresectable
No distant metastases	No distant metastases	Distant metastases (including non-regional lymph node metastases)
No arterial tumor contact of CA, SMA, or CHA	Pancreatic head/uncinate process: Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. Solid tumor contact with the SMA ≤180° Solid tumor contact with variant arterial anatomy Pancreatic body/tail: Solid tumor contact with the CA of ≤180° Solid tumor contact with the CA >180° without involvement of the aorta and with intact and uninvolved GDA	Pancreatic head/uncinate process: Solid tumor contact with SMA >180° Solid tumor contact with CA >180° Solid tumor contact with the first jejunal SMA branch Pancreatic body/tail: Solid tumor contact of >180° with the SMA or CA Solid tumor contact with CA and aortic involvement
No tumor contact with the SMV or PV or ≤ 180° contact without vein contour irregularity	Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein but with suitable vessel proximal and distal to the site of involvement Solid tumor contact with the IVC	Pancreatic head/uncinated process: Unreconstructible SMV/PV due to tumor involvement or occlusion Contact with most proximal draining jejunal branch into SMV Pancreatic body/tail: Unreconstructible SMV/PV due to tumor involvement or occlusion

CA Celiac axis, *SMA* Superior mesenteric artery, *CHA* Common hepatic artery, *SMV* Superior mesenteric vein, *PV* Portal vein, *GDA* Gastroduodenal artery, *IVC* Inferior vena cava

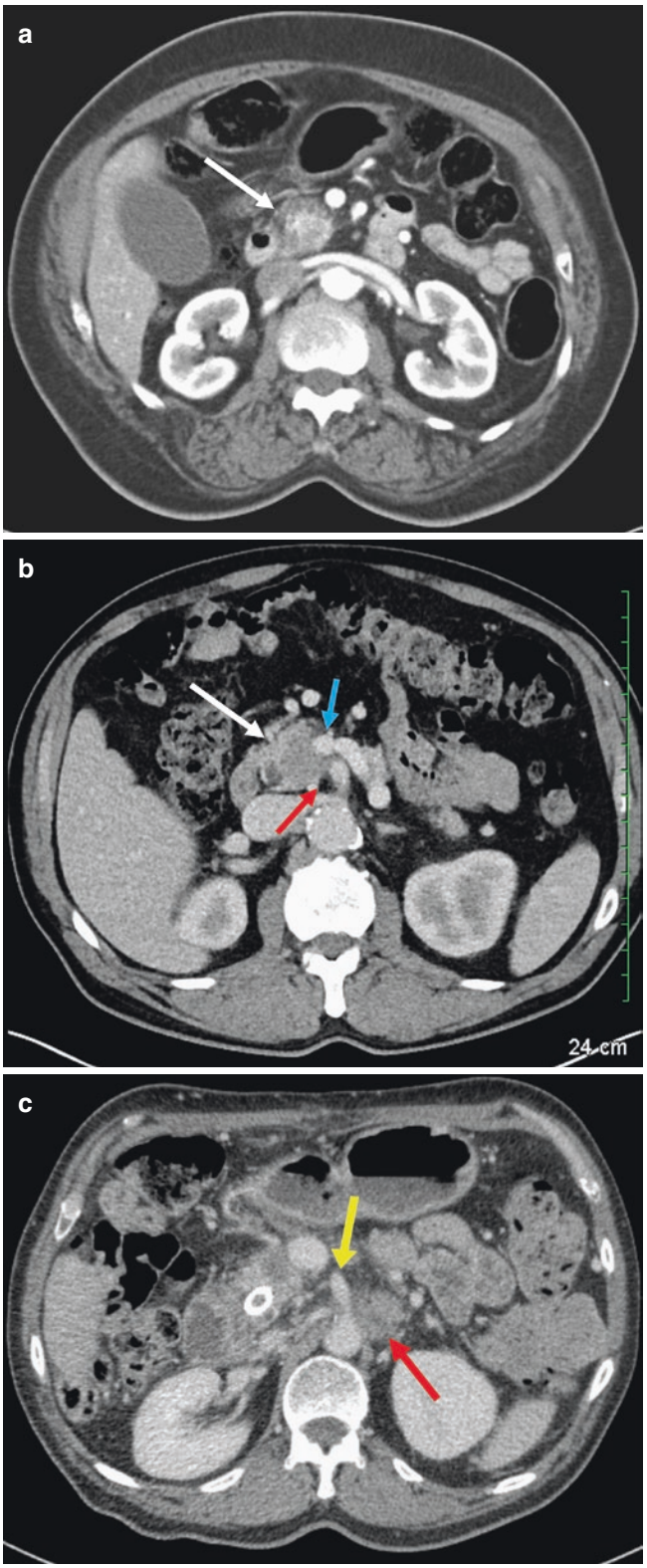


Fig. 14.1 Examples of resectable (**a**), borderline (**b**), and unresectable (**c**) pancreas adenocarcinoma on computed tomography. White arrow indicates primary tumor. (**a**) The mass (white arrow) involves <180° of the superior mesenteric vein and does not touch the superior mesenteric artery. (**b**) The mass (white arrow) involves >180° of the superior mesenteric vein (blue arrow) and <180° of the superior mesenteric artery (red arrow). (**c**) There is narrowing of the origin of the superior mesenteric artery (yellow arrow) and soft tissue to the left side of the aorta (red arrow)

Disease Staging

The staging evaluation for PDAC is centered around contrast-enhanced CT scan, which is used to assess for metastatic disease and to delineate the relationship of the tumor to surrounding structures, including the mesenteric vasculature. CT scan has long been considered the "gold standard" in evaluation of pancreas cancer, due to its wide availability, ease of interpretation, and excellent negative predictive value for unresectability [21]. Three- to five-millimeter cuts are obtained following tri-phasic contrast administration; intravenous (IV) contrast is given and images are obtained in both an arterial and a portal venous phase, and a neutral or low-density oral contrast agent (often water) is given in order to distend the stomach and duodenum, but not interfere with evaluation of the vasculature, which would likely happen if high-density oral contrast were given [22]. The portal venous phase is particularly important because it is in this phase that the pancreatic parenchyma enhances best, in contrast with the typically hypodense appearance of PDAC.

There are two main limitations of CT scan for staging. First is the detection of micrometastatic disease that could only be found with increased resolution images. The liver is the most common location for metastasis, and contrast-enhanced CT scan generally is excellent at detecting hepatic disease; however, smaller lesions are not as well evaluated, and the sensitivity for detection decreases with decreasing lesion size [23]. Microscopic peritoneal implants are also not well visualized on CT scan. An estimated 15–40% of patients initially thought to be resectable based on axial imaging are found to have metastatic disease on laparotomy [24–27]. The other main shortcoming of CT is the inconsistent correlation between relationship of tumor to mesenteric vasculature on scans and the actual relationship once in the operating room [28], and this can impact the ability to achieve an R0 resection. In an R1 resection, margin positivity is most commonly at the mesenteric or retroperitoneal margin [29], further highlighting the importance of accurate pretreatment cross-sectional imaging.

CT interpretation is also operator-dependent and is best done by radiologists who are experts in pancreas cancer imaging. Studies have shown that specialized radiologists more accurately interpret scans within their own areas of expertise [30], and these radiologists are more likely to be based in larger centers. In a retrospective review of PDAC patients at a single center, Walters et al. concluded that pancreas-protocol imaging at a high-volume center improves preoperative staging and can alter disease management [27]. Interestingly, they found that more than 50% of patients who presented to their center with prior imaging were reimaged with a resulting change in management strategy.

Multiple adjuncts to CT scan have been proposed in order to more thoroughly stage a newly diagnosed pancreas cancer patient. These adjuncts include the use of endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and

positron emission tomography (PET)/CT. In patients who present with classic signs of pancreas cancer (obstructive jaundice, unexplained weight loss, abdominal pain, new onset pancreatitis) but have equivocal CT findings, EUS is of benefit as it is much more sensitive than CT scan in the diagnosis of lesions smaller than 2 cm (90% versus 40%) [31]. Tumor relationship to the surrounding vasculature and regional lymph nodes is accurately assessed by EUS, which facilitates appropriate staging. It has also become the modality of choice to obtain a tissue diagnosis in patients with borderline resectable tumors who are to undergo neoadjuvant therapy, as well as restaging borderline resectable and locally advanced tumors after the completion of neoadjuvant treatment, in order to assess for cellular necrosis along the periphery of tumors where they abut the vasculature. A recent meta-analysis of data spanning a 14-year period found the overall sensitivity and specificity of EUS-fine-needle aspiration (FNA) for diagnosing a solid pancreas mass to be 86.8% and 95.8%, respectively [32]. Limitations of this imaging modality are that it is highly operator-dependent and has an approximately 1–2% risk of complications, which include post-procedural pancreatitis, bleeding, or duodenal perforation [33]. Another imaging modality gaining wider acceptance is MRI. It has greater soft-tissue contrast when compared with CT [34] and so is excellent for small or isoattenuating tumors [35], and magnetic resonance cholangiopancreatography (MRCP) provides precise definition of the main pancreatic duct and biliary tree, which is especially useful for small, non-contour-deforming pancreatic masses [36].

PET/CT can be used as an adjunct after high-quality pancreas protocol CT is obtained, particularly in patients deemed to be high risk for having extra-pancreatic disease (borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes) [15]. It should not be considered a substitute for high-quality cross-sectional imaging.

Diagnostic staging laparoscopy can be used to look for metastases that are not evident on cross-sectional imaging. Timing can be prior to initiation of chemoradiation or surgery, again in patients considered to be high risk for metastases.

Although the vast majority of patients are still diagnosed and staged by CT scan, continued advances in all imaging modalities with resulting higher resolution will undoubtedly lead to earlier diagnosis and treatment of patients with PDAC. Choice of diagnostic study should be tailored to each specific clinical scenario.

Resectable Pancreas Cancer

Adjuvant Therapy

Surgery with curative intent remains standard of care for upfront resectable pancreas cancer. Unfortunately, even with an R0 resection, the vast majority of patients will go on to develop local, regional, or systemic recurrence and eventually die from their disease [37], demonstrating that surgery alone is inadequate for long-term survival. This observation is the basis for the intense interest in the development of multimodal therapeutic strategies to aid in both locoregional and systemic control of PDAC. Margin status at resection is an important predictor of overall survival, and it follows that adjuvant therapy with emphasis on locoregional control could have survival benefit. Neoadjuvant and adjuvant chemoradiation has been shown to improve overall survival in other surgically resected gastrointestinal (GI) tract malignancies, including gastric/gastroesophageal (GE) junction and rectal cancers [38, 39]. In pancreas cancer, older studies focused on palliation of unresectable pancreas cancer demonstrated benefit to radiation therapy, often combined with 5-fluorouracil (5-FU) [40, 41], and this was the basis for the Gastrointestinal Tumor Study Group (GITSG) trial—the first prospective, randomized phase III trial evaluating adjuvant chemoradiation following surgical resection of PDAC.

The GITSG trial was the first of three "split-course" adjuvant chemoradiation therapy trials [42], and it was designed to deliver a split-course of 40 Gy external beam radiation therapy (EBRT) over 6 weeks, including a 2-week break from radiation therapy after administration of the first 20 Gy, along with 5-FU administration both during radiation therapy and subsequently as a weekly maintenance infusion for 2 years or until documented disease progression. It enrolled 43 patients who had undergone an R0 surgical resection of ductal, acinar, or undifferentiated pancreas adenocarcinoma, and excluded patients with periampullary, islet, and cystadenocarcinoma. Twenty-one patients were randomized to undergo adjuvant chemoradiation with 5-FU, while the other 22 were randomized to observation. The trial showed a statistically significant doubling of median survival in the treatment group compared with the controls (20 months versus 11 months) and a modest improvement in 5-year survival (19% versus 5%). Adjuvant therapy was well-tolerated among participants. This study was limited by its small size causing it to be underpowered and by the fact that almost 40% of the treatment arm patients (8/21) did not complete their maintenance therapy. It was stopped early due to the slow accrual and the evolving survival differences between groups. In an attempt to increase power, the investigators later added another nonrandomized cohort of 30 patients to the same treatment algorithms and found similar results [43]. The encouraging results from the GITSG study are the foundation for adjuvant chemoradiation as a standard of care for surgically resected PDAC in the United States.

The GITSG trial was followed by the European Organization for Research and Treatment of Cancer (EORTC) group trial, first published in 1999 in *Annals of Surgery* [44]. In this study, 207 surgically resected patients were again randomized to undergo either observation or adjuvant chemoradiation in a similar "split-course" manner and also utilizing 5-FU. Although this adjuvant regimen was

again shown to be well-tolerated, no statistically significant survival differences were seen between groups, and the investigators concluded that adjuvant chemoradiation could not be recommended. Important differences between EORTC and GITSG deserve mention, most notably the inclusion of patients with positive pathologic margins in the EORTC study, and also the EORTC inclusion of nonpancreatic periampullary adenocarcinomas—a group of tumors with a known better overall prognosis. In response to these concerns, the authors included a subset analysis of 114 patients with head of pancreas cancer only but still were unable to demonstrate any benefit to adjuvant chemoradiation and in fact concluded that adjuvant chemoradiation with 5-FU, although well-tolerated, is not indicated. European centers have cited this study, as well as the following European Study Group for Pancreatic Cancer (ESPAC) study, when recommending against adjuvant chemoradiation in their practice policies.

In an effort to delineate a role for adjuvant chemotherapy in resected PDAC after having found disappointing results from adjuvant chemoradiation in European centers, the ESPAC-1 trial was conducted. It was a multicenter trial in 2 × 2 factorial fashion in which 289 patients with resected pancreas ductal adenocarcinoma (irrespective of margin status) were randomly assigned to undergo observation (69 patients), or adjuvant chemoradiation alone (73 patients), chemotherapy alone (75 patients), or chemoradiation followed by chemotherapy (72 patients). It was again a "split-course" design, and 5-FU was utilized as the chemotherapeutic regimen. The median follow-up was 47 months, and the results were published in the *New England Journal of Medicine* in 2004 [45]. The study has been critiqued for its complex design making it difficult to interpret, but the authors came to two major conclusions: that (1) adjuvant chemotherapy had a significant survival benefit (21% 5-year survival versus 8% for those who underwent observation, $p = 0.009$) and that (2) adjuvant therapy did not show benefit and actually had a deleterious effect on survival (10% versus 20% 5-year survival in the chemoradiation versus no chemoradiation group, $p = 0.05$). The authors postulated that chemoradiation may have been detrimental both because it delayed the onset of systemic chemotherapy, and because the "split-course" algorithm allowed for a break in treatment that could result in disease progression. Critics of this study have emphasized the lack of standardization and quality assurance of the radiation therapy protocols utilized (and this critique has also been made of the GITSG and EORTC trials, as radiation therapy standards have markedly improved since GITSG was first published in 1985). Many patients received varying doses of radiotherapy, and there was no centralized review of technique or protocol. Additionally, the study was not actually powered to derive comparisons among the four arms of the 2 × 2 randomization design. Although it has sparked much controversy with regard to the role for adjuvant radiation therapy in resected PDAC, ESPAC-1 has helped to solidify a role for 5-FU-based chemotherapy in adjuvant setting.

In 1997, Burris et al. published a landmark study in the treatment of advanced pancreas cancer. They demonstrated that single-agent gemcitabine not only improved quality of life in patients with unresectable pancreas cancer (better pain control, increased performance status), but also had a modest survival advantage over treatment with 5-FU. The latter was given using an intravenous bolus schedule. This was the first time in 30 years that a new chemotherapeutic agent was shown to have improved survival benefit when compared with 5-FU; gemcitabine also had a favorable toxicity profile [46]. This paved the way for the Charite-Onkologie or CONKO-001 study, a European multicenter, phase III randomized controlled trial of adjuvant gemcitabine versus observation after curative-intent resection of PDAC [37]. In this trial, 368 patients, who had undergone either R0 or R1 resection of their pancreas cancer and who had not undergone any neoadjuvant therapy, were stratified according to resection status (R0 versus R1), tumor (T) status (T1-2 versus T3-4), and nodal (N) status (negative versus positive). They were then randomized to undergo adjuvant gemcitabine for 6 cycles ($n = 179$) or observation ($n = 175$). Primary endpoint was median disease-free survival, and a statistically significant survival benefit was seen with gemcitabine therapy (13.4 months compared with 6.9 months, $p < 0.001$), almost double that of the observation group. This survival benefit was seen regardless of margin, T, or nodal status. Upon initial publication, there was no overall survival benefit to the administration of gemcitabine therapy (median survival 22.1 months gemcitabine versus 20.2 months control), but a modest yet statistically significant overall survival benefit was seen when the data were updated in 2008 at the annual American Society of Clinical Oncology (ASCO) meeting (22.8 months versus 20.2 months, $p = 0.05$, and estimated 5-year survival 21% versus 9%) [47]. This study established single-agent gemcitabine as the backbone of adjuvant therapy in resected pancreas adenocarcinoma.

Around the same time that CONKO-001 was underway in Europe, North American centers began to enroll patients in the Radiation Therapy Oncology Group (RTOG) 97-04 trial [48]. This was a multicenter, randomized controlled phase III trial also designed to evaluate gemcitabine in the adjuvant setting. Patients with grossly resected pancreas adenocarcinoma were then randomized to undergo either 5-FU or gemcitabine chemotherapy, and treatment in both groups was then followed by 5-FU-based chemoradiation. This was in keeping with the accepted standard of care in North America that utilized adjuvant chemoradiation, based on the initial GITSG trial. Patients were stratified according to tumor diameter (<3 cm or >3 cm), nodal status (positive or nega-

Table 14.2 Summary of randomized controlled adjuvant trials for resected pancreas cancer

Trial	Comparison	Agents	Patient Population	Median Survival	*p* value
GITSG [42] 1985	CRT vs Obs	40 Gy + 5-FU	*n* = 21 vs 22	20 vs 11 mo	0.035
EORTC [44] 1999	CRT vs Obs	40 Gy + 5-FU	*n* = 60 vs 54	17 vs 13 mo	0.099
ESPAC-1 [45] 2004	CRT vs no CRT CT vs no CT	20 Gy + 5-FU 5-FU	*n* = 145 vs 144 *n* = 147 vs 142	16 vs 18 mo 20 vs 16 mo	0.05 0.009
CONKO-001 [37] 2007	CT vs Obs	gem	*n* = 179 vs 175	13 vs 7 mo	<0.001
RTOG 97-04 [48] 2008	CT + CRT vs CT + CRT	5-FU + 50.4 Gy/5-FU gem +50.4 Gy/5-FU	*n* = 201 vs 187	17 vs 20.5 mo	0.09
ESPAC-3 [49] 2010	CT vs CT	gem vs 5-FU	*n* = 537 vs 551	24 vs 23 mo	0.39
JASPAC 01 2016 [53]	CT vs CT	S-1 vs gem	*n* = 192 vs 193	46.5 vs 25.5 mo	<0.0001
ESPAC-4 2017 [50]	CT vs CT	gem vs gem/cape	*n* = 366 vs 364	25.5 vs 28 mo	0.032

Abbreviations: *CRT* chemoradiation, *Obs* observation, *CT* chemotherapy, *5-FU* 5-fluorouracil, *gem* gemcitabine, *cape* capecitabine

tive), and surgical margins (positive, negative, or unknown). On analysis of 451 patients, the investigators found no difference in overall or disease-free survival between the 2 treatment groups. However, they further analyzed a subset of pancreatic head tumors ($n = 388$) and found a trend toward increased median survival and increased 3-year survival in the gemcitabine group (20.5 months and 31% 3-year survival in gemcitabine versus 16.9 months and 22% for fluorouracil, $p = 0.09$); when adjusted for the aforementioned stratification variables, this trend became statistically significant ($p = 0.05$). The authors concluded that when added to 5-FU-based chemoradiation, adjuvant gemcitabine-based chemotherapy was superior to 5-FU-based chemotherapy. This study did not evaluate the role of adjuvant chemoradiation because it was given to both groups, but it further bolstered the call for gemcitabine in the adjuvant setting.

With new information from CONKO-001 calling for single-agent gemcitabine as the backbone of adjuvant therapy, the next logical step was to directly compare gemcitabine versus 5-FU, recognizing that results from ESPAC-1 showed a survival benefit of 5-FU-based chemotherapy. European investigators thus designed the ESPAC-3 trial that was published in *JAMA* in 2010 [49]. This study randomized 1088 patients who had undergone R0 or R1 resection of PDAC to then undergo 6 months of either 5-FU or gemcitabine. The primary endpoint was overall survival, which was the same between groups (23.0 versus 23.6 months, respectively); and the authors concluded that the 2 agents were essentially equivalent. Both are reasonable options, but gemcitabine, with its favorable side effect profile and ease of administration (on a weekly basis versus every day for a week at a time for 5-FU), has become the cornerstone of adjuvant therapy for resected PDAC. Most recently, the ESPAC-4 trial compared gemcitabine to gemcitabine with capecitabine. Seven hundred thirty patients were randomized in this phase III trial and found an improvement in median overall survival of 28 versus 25.5 months, $p = 0.032$ [50].

Gemcitabine is also known to be an excellent radiosensitizer [51], and other groups have sought to utilize this trait. Van Laethem et al. have conducted a randomized phase II trial comparing gemcitabine plus gemcitabine-based chemoradiation to gemcitabine alone in the adjuvant setting [52] and found the former to be safe and well-tolerated. Median overall survival in both groups was 24 months, but interestingly there was a statistically significant improvement in local control with the incorporation of chemoradiation. The authors have advocated for a phase III trial to further investigate multimodal gemcitabine. A summary of key randomized controlled trials of adjuvant therapy for resectable pancreas cancer is seen in Table 14.2 [37, 42, 44, 45, 48–50, 53].

The next steps in the advancement of adjuvant therapy involve combinations of cytotoxic therapies and potentially the addition of targeted therapies to conventional chemotherapeutic and/or chemoradiation regimens. Many new trials of combination adjuvant therapy have drawn on modest albeit real successes in the management of locally advanced or metastatic pancreas cancer. Moore et al. [54] found a statistically significant survival benefit in adding erlotinib (an epidermal growth factor receptor [EGFR] tyrosine kinase inhibitor) to gemcitabine in this unresectable patient population in a randomized, phase III trial. Other groups have investigated agents such as tipifarnib, bevacizumab, and cetuximab in various combinations with gemcitabine and also in patients with unresectable disease, but have found no benefit to date over that of gemcitabine alone [55]. To date, no targeted agent has been proven to be of value in the adjuvant setting, but new clinical trials continue to accrue resected patients in an effort to improve on the poor 5-year survival rates seen even after a complete surgical resection. A summary of ongoing adjuvant phase III clinical trials for resectable pancreas cancer is seen in Table 14.3.

Currently, adjuvant systemic chemotherapy is recommended for all patients capable of receiving it. For those

Table 14.3 Summary of ongoing adjuvant Phase III trials for pancreas adenocarcinoma

Trial	NCT Number	Comparison	Agents	Patient Enrollment	Current Status	Primary endpoint
RTOG 0848	01013649	CT vs CT + CRT	gem +/− erlot vs gem +/− erlot with 5FU or cape-XRT	$n = 950$	Recruiting	Overall survival
APACT	01964430	CT vs CT	gem vs gem + N-pac	$n = 866$	Active, not recruiting	Disease-free survival
Adjuvant gem vs neoadjuvant and adjuvant FOLFIRINOX	02172976	CT vs CT	gem vs FOLFIRINOX	$n = 126$	Recruiting	Overall survival
Italian multicenter study	02355119	CT vs CT	gem vs FOLFOXIRI	$n = 310$	Recruiting	Disease-free survival

Abbreviations: *CRT* chemoradiation, *Obs* observation, *CT* chemotherapy, *5-FU* 5-fluorouracil, *gem* gemcitabine, *cape* capecitabine, *erlot* erlotinib, *XRT* radiation, *N-pac* Nab-paclitaxel

patients who received neoadjuvant therapy, adjuvant chemotherapy is still recommended with dosing and regimen based on the degree of response to neoadjuvant treatment.

Neoadjuvant Therapy

It has become increasingly evident that pancreas cancer is a systemic disease at the time of diagnosis, as evidenced by continued poor overall survival in patients who have undergone an R0 resection and completed adjuvant therapy. Not only has this reinforced the importance of multimodal therapy for both local and systemic disease control, but it has also brought to the forefront an interest in neoadjuvant treatment strategies. Proponents of neoadjuvant therapy for resectable PDAC cite several potential benefits. First is the early delivery of systemic therapy that is generally well-tolerated and completed. Multiple studies have shown that up to 25% of patients who undergo surgical resection never complete their adjuvant treatment [44, 56, 57], due to prolonged recovery, postoperative complications, or patient refusal. A neoadjuvant approach would ensure that nearly all patients who are to undergo an operation have had the benefit of systemic therapy. It would additionally allow patients with aggressive tumor biology whose disease progresses during neoadjuvant therapy, or those whose functional status does not tolerate therapy, to self-select themselves as patients who will not benefit from surgery and thus avoid the potential morbidity of a major pancreatic resection. Another benefit is the enhanced cytotoxic effect seen with delivery of chemoradiation to undisturbed, well-oxygenated tissue. Perhaps most important is the potential for preoperative chemotherapy and/or radiation to downsize disease. Neoadjuvant therapy also treats the local nodal basin, and all of the above will in turn improve the rate of R0 resection and also decrease locoregional recurrence. Lastly, several groups have demonstrated a decreased pancreaticojejunal anastomotic leak rate in patients who have undergone neoadjuvant chemoradiation [58, 59].

Potential drawbacks to neoadjuvant therapy warrant mention. Chemotherapy administration requires a tissue diagnosis prior to its initiation. Tumor sampling is commonly done via endoscopic ultrasound (EUS) with fine-needle aspiration (FNA), but this technique remains highly operator-dependent and often requires patients at small outlying centers to be evaluated and treated elsewhere. Additionally, patients who present with jaundice and biliary obstruction need to undergo biliary tree decompression prior to starting chemotherapy. In 1998, a phase II multi-institutional neoadjuvant trial conducted by members of the Eastern Cooperative Oncology Group (ECOG), [60] in which 50% of enrolled patients required pretreatment biliary decompression, cited a high level of stent-related morbidity and mortality. The authors raised concerns for the safety of pretreatment biliary stenting, potentially making neoadjuvant therapy unsafe in this patient population. These concerns were addressed in a larger-scale study out of MDACC, which demonstrated low rates of hepatic toxicity and biliary stent-related complications in patients undergoing neoadjuvant chemoradiation [61]. Larger diameter stents, close patient follow-up, and a single-institution study design utilizing a single experienced endoscopist to manage stents were all felt to contribute to the low complication rates. A final potential drawback of neoadjuvant therapy is that it delays definitive surgical management. Interestingly though, patients whose disease progresses during neoadjuvant treatment most commonly also have distant metastases as opposed to local progression alone [62–65], and thus an upfront operation would not have provided adequate disease control in this group of patients.

Neoadjuvant therapy for resectable pancreas cancer was first trialed and shown to be both safe and feasible in the early 1990s. Evans et al. enrolled 28 patients with histologically proven localized pancreatic head adenocarcinoma to undergo a regimen of 5-FU and 50.4 Gy over 5 ½ weeks [64]. All patients completed their neoadjuvant therapy, demonstrating that it was safe and well-tolerated. Upon restaging, five patients had developed metastatic disease, and they were spared a subsequent operation. Seventeen patients underwent resection, and all tumor specimens had evidence of tumor cellular injury imparted by chemoradiation. This study was the basis for another trial out of MDACC pub-

lished in 1998 by Pisters et al. [65]. The most debilitating side effect of the chemoradiation regimen from the Evans et al. trial [64] was GI toxicity, requiring hospital admission in 32% of patients. In an effort to ameliorate this problem, the investigators decreased the length of therapy from 5 ½ down to 2 weeks, with a higher dose per fraction of radiation received, in this "rapid fractionation" trial. All 35 patients enrolled had resectable pancreatic head cancer, and all 35 completed their chemoradiation. Surgical resection combined with external beam intraoperative radiation therapy (EB-IORT) was completed in 74% of patients taken for laparotomy, and this study demonstrated not only minimal toxicity of the chosen chemotherapeutic regimen but also excellent locoregional disease control.

Other groups have investigated the addition of mitomycin C (MMC) to a regimen of infusional 5-FU and external beam radiation therapy. A phase II trial out of Fox Chase Cancer Center [66] treated 31 patients with biopsy-proven pancreatic or duodenal carcinoma with this regimen. All but two patients completed their neoadjuvant therapy, and 38% of the pancreatic cancer patients were able to be resected; all of these patients had negative pathologic margins. The authors concluded that this combination treatment was safe and resulted in improved locoregional disease control. An ECOG phase II trial published in 1998 evaluated and treated 53 PDAC patients with the same regimen. Despite over half of the patients requiring hospital admission related to treatment toxicity, most commonly due to biliary complications, the study established both the safety and the feasibility of neoadjuvant therapy in a cooperative setting [60]. It should be mentioned that the aforementioned studies by Yeung and Hoffman included patients with both resectable and locally advanced cancers, potentially confounding results.

With the establishment of the safety and feasibility of a neoadjuvant strategy, the next logical step has been to determine if it provides a survival advantage over adjuvant therapy. This was first addressed by Spitz et al. [57] who analyzed 142 patients with potentially resectable pancreatic head or periampullary adenocarcinoma at MDACC over a 5-year period. Ninety-one patients underwent neoadjuvant 5-FU-based chemoradiation, and the other 51 patients proceeded first to surgery. In order to be included in the neoadjuvant group, patients were required to have a hypodense mass in the head of the pancreas, as well as biopsy-proven adenocarcinoma. Of the 91 neoadjuvant patients, 24 (26%) had disease progression prior to surgery and were thus spared the potential morbidity of an operation. Forty-one of the remaining 67 patients (61%) were treated according to planned protocol, and their median survival was 19.2 months. In the adjuvant group, 42 of 51 (82%) underwent pancreaticoduodenectomy, and 25 of those patients were found to have adenocarcinoma of pancreatic origin. Seventy-six percent of this cohort (19/25) completed their adjuvant therapy, whereas 24% (six patients) did not. The median survival for these 19 adjuvant patients was 22 months and thus there was no statistically significant survival difference between groups. A critique of this study is its selection bias—in order to receive neoadjuvant therapy, patients had to have both a tissue diagnosis of cancer and a mass on CT scan (likely these tumors were larger and more locally advanced). Although no survival benefit was seen, the authors did again demonstrate the safety and feasibility of a neoadjuvant regimen, and concluded that chemotherapy administered in rapid-fractionation as opposed to standard-fractionation was better tolerated with a significantly shorter treatment duration.

The establishment of gemcitabine as an effective agent in the adjuvant setting has led to its investigation preoperatively in various combinations. Talamonti et al. first trialed full-dose neoadjuvant gemcitabine in 3 cycles and in combination with radiation therapy in a multi-institutional phase II study published in 2006 [67]. In this study, 19 of 20 patients (95%) completed their neoadjuvant therapy without interruption and with minimal side effects, and 17 of the original 20 patients (85%) were able to undergo resection, with negative margins in 94% and uninvolved lymph nodes in 65%, suggesting a significant gemcitabine treatment effect. The median overall survival was 26 months. A larger phase II trial out of MDACC then enrolled 86 patients with resectable pancreas adenocarcinoma and treated them with 7 weekly gemcitabine infusions in combination with 30 Gy rapid-fractionation radiation therapy [68]. After accounting for disease progression, 64 of 86 patients (74%) were able to undergo successful pancreaticoduodenectomy. Median overall survival for the resected group was 34 months, whereas the remainder of patients (those whose disease had progressed on neoadjuvant therapy, and those who were explored and found to be metastatic) had an overall survival of only 7 months. At the time of its publication, the 34-month median survival seen in the neoadjuvant group was a significant improvement over other studies and has reinforced the effectiveness of gemcitabine as well as helped to bolster the argument for a neoadjuvant approach to multimodal therapy.

Promising results of neoadjuvant gemcitabine have prompted its combination with other chemotherapeutic agents, the rationale being that when most resected patients recur their disease is systemic, and additional cytotoxic drugs could provide better systemic control. Based on the encouraging results of a small phase II study of 42 patients with locally advanced, unresectable, or metastatic PDAC that showed combination gemcitabine-cisplatin was overall well-tolerated and had greater disease activity than single-agent gemcitabine [69], gemcitabine was then trialed in combination with cisplatin in the neoadjuvant setting by

Varadhachary et al. [70]. Ninety patients were enrolled in this study, and 79 (88%) completed their neoadjuvant gemcitabine, cisplatin, and rapid-fractionation gemcitabine chemoradiation. After restaging, 62 of 79 patients (78%) were explored and of those 52 patients (66%) underwent pancreaticoduodenectomy. The median survival for these 52 patients was 31 months, which was similar to the 34-month median survival seen by Evans et al. in their neoadjuvant gemcitabine group [68]. The authors concluded that combination gemcitabine-cisplatin did not improve survival over that of gemcitabine alone. Full-dose gemcitabine has also been trialed in combination with oxaliplatin and radiation therapy in a study out of the University of Michigan [71]. This study included 68 patients with both resectable and borderline resectable tumors. Neoadjuvant therapy was completed in 90% of patients (61 of 68), with a resultant 63% of patients undergoing resection (43 of 68 patients) and of those, 84% (36 of 43) were able to have an R0 resection. Median overall survival was 18.2 months for all patients, 27.1 months for all resected patients, and 34.6 months for those having had an R0 resection. The regimen was well-tolerated, and the authors were encouraged with the results, notably because of the high percentage of borderline resectable patients (39 of 68 patients, or 57%) included.

Neoadjuvant chemotherapy for resectable PDAC has also been evaluated without concurrent radiation therapy. In a randomized phase II European trial, Palmer et al. [72] enrolled 50 patients with potentially resectable disease and randomized them to receive either gemcitabine (24 patients) or gemcitabine plus cisplatin (26 patients), with the primary outcome being rate of resection. Tolerance to the regimens was similar between groups, and of the 27 patients that underwent resection, 9 of those (38%) had received gemcitabine alone, whereas 18 (70%) were from the combination arm. The authors concluded that gemcitabine plus cisplatin may be a more efficacious strategy and warrants further investigation. Heinrich et al. [73, 74] then published results of another European trial of neoadjuvant gemcitabine plus cisplatin. This phase II trial included 28 patients with histologic confirmation of pancreas cancer, all of which were potentially resectable. Patients underwent 4 biweekly cycles of gemcitabine and cisplatin and then were restaged, and primary endpoint was resectability rate. Upon restaging, 26 of 28 patients (93%) were able to proceed to surgery and 25 of those patients (89%) underwent pancreaticoduodenectomy, with an R0 resection rate of 80%. The trial is unique in its evaluation of histologic tumor response, which was shown to be similar to other chemoradiation protocols. Again, neoadjuvant chemotherapy was shown to be well-tolerated. Finally, a recent phase II trial out of Memorial Sloan-Kettering [75] sought to evaluate neoadjuvant gemcitabine in combination with oxaliplatin, without chemoradiation and then followed by adjuvant gemcitabine in 38 patients with resectable pancreas cancer. Ninety-two percent of the patients completed neoadjuvant therapy, and the resectability rate was 71% (27 of 38 patients), demonstrating that the regimen was well-tolerated and resulted in similar resection rates as other trials. A summary of selected neoadjuvant therapy trials is seen in Table 14.4 [60, 64–68, 70, 71, 74–80].

Table 14.4 Summary of selected neoadjuvant trials for resectable and borderline resectable pancreas cancer

Trial	Regimen	Agents	Patient Population	Preoperative Staging	% Resected	% R0	Median Survival after Resection (months)
Evans et al. (1992) [64]	CRT	50.4 Gy + 5-FU	*n* = 28	R	61	82	NA
Yeung et al. (1993) [66]	CRT	50.4 Gy + 5-FU + MMC	*n* = 26	R, LA	38	100	NR
Pisters et al. (1998) [65]	CRT + IORT	30 Gy + 5-FU + IORT	*n* = 35	R	57	90	25 mo
Hoffman et al. (1998) [60]	CRT	50.4 Gy + 5-FU + MMC	*n* = 53	R, LA	45	67	16 mo
Talamonti et al. (2006) [67]	CT + CRT	gem; 36 Gy + gem	*n* = 20	R	85	94	26 mo
Evans et al. (2008) [68]	CRT	30 Gy + gem	*n* = 86	R	74	89	34 mo
Varadhachary et al. (2008) [70]	CT + CRT	gem, cis; 30 Gy + gem	*n* = 90	R	58	96	31 mo
Kim et al. (2013) [71]	CRT	30 Gy + gem + ox	*n* = 68	R, BR	63	84	27 mo
Heinrich et al. (2008) [74]	CT	gem + cis	*n* = 28	R	89	80	19 mo
O'Reilly et al. (2014) [75]	CT	gem + ox	*n* = 38	R	71	74	22 mo (recurrence-free survival)
Mehta et al. (2001) [76]	CRT	50.4 to 56 Gy + 5-FU	*n* = 15	BR	60	100	30 mo
Small et al. (2008) [77]	CRT	36 Gy + gem	*n* = 39	R, BR, LA	44	NA	NA
Brown et al. (2008) [78]	CRT + CT	50.4 Gy + either 5-FU, gem, cap or bev; gem, gem/ox, gem/erlot, gem/bev, 5-FU/erlot	*n* = 13	BR	100	85	NR
Stokes et al. (2011) [79]	CRT	50 Gy + cap	*n* = 40	R, BR	40	75	12
Chuong et al. (2013) [80]	CRT + CT	SBRT + gem; gem/doce/cap	*n* = 57	BR	56	97	19 mo

Abbreviations: *CRT* chemoradiation, *CT* chemotherapy, *5-FU* 5-fluorouracil, *gem* gemcitabine, *MMC* mitomycin-C, *IORT* intraoperative radiation therapy, *cis* cisplatin, *ox* oxaliplatin, *cap* capecitabine, *bev* bevacizumab, *erlot* erlotinib, *doce* docetaxel, *R* resectable, *BR* borderline resectable, *LA* locally advanced, *R0* R0 resection, *NA* not available, *NR* not reached

The collective body of evidence with regard to neoadjuvant strategies for resectable pancreas cancer has established two main conclusions. First, the majority of regimens are safe and feasible, with acceptable side effect profiles. Second, when analyzing these small and mostly nonrandomized trials, neoadjuvant therapy results have comparable survival to that of adjuvant therapy. Proponents of a neoadjuvant approach thus cite these facts in addition to the aforementioned theoretical benefits of neoadjuvant treatment (tumor downstaging, treatment of micrometastatic disease, enhanced delivery of cytotoxic agents to healthy tissues, self-selection of unhealthy patients or patients with aggressive tumor biology who will not benefit from an operation, completion of multimodal therapy), as well as the knowledge that 25% of patients who are supposed to undergo adjuvant therapy are unable to do so. Interpretation of the many neoadjuvant trials, however, must be done with the understanding that much of the survival data is not based on intent-to-treat analyses. Regardless, neoadjuvant therapy certainly is not harmful and does not result in inferior survival.

Unlike adjuvant chemotherapy, neoadjuvant therapy is not standard of care for *resectable* pancreas cancer. It does, however, have a role particularly in high-risk resectable disease (large primary tumor, markedly elevated CA 19-9, large regional lymph nodes, extreme weight loss, extreme pain) or when a clinical trial is available.

Borderline Resectable Pancreas Cancer

Neoadjuvant Therapy

The emergence of borderline resectable pancreas cancer as a spectrum of tumors that, although potentially resectable, have a high likelihood of margin positivity has made neoadjuvant therapy for this group very attractive and rational. As the major driver of overall survival is the ability to achieve an R0 resection, neoadjuvant therapy offers a theoretical advantage. Confirmation of this advantage, however, has been difficult for several reasons. First, available published trials are mostly small-scale, single-institution retrospective studies. Many of these studies have used different chemotherapeutic agents, which also makes it difficult to compare across studies. Finally and most importantly has been the lack of a standardized definition and staging of borderline resectable disease (see Table 14.1). This has resulted in borderline resectable patients being included in trials of both resectable and locally advanced unresectable disease, confounding results. Despite these shortcomings and the paucity of prospective data, neoadjuvant therapy is currently the preferred initial management for patients with borderline resectable PDAC [81]. The impetus now is on the acceptance of a standardized definition and staging of these borderline PDACs, in order to isolate and study this group of patients accordingly.

The first prospective case series of neoadjuvant therapy for borderline resectable PDAC was published in 2001 by Mehta et al. out of Stanford [76]. In this study, 15 patients with "marginally resectable" pancreas cancer, defined as lesions in which the perivascular fat plane was absent over 180° of the SMA, SMV, or PV and persisted for a length of greater than 1 cm, underwent neoadjuvant treatment with 50.4 to 56 Gy and infusional 5-FU. All patients completed their chemoradiation, and upon restaging, 60% (9 of 15 patients) underwent pancreaticoduodenectomy, and all resected patients had negative margins. Overall median survival was 12 months and for the resected group was 30 months. This study demonstrated that neoadjuvant therapy in marginally resectable tumors was safe and well-tolerated, with the potential to downstage tumors.

Landry et al. [82] published the first multi-institutional, prospective randomized phase II trial of neoadjuvant therapy for borderline resectable PDAC. They used a slightly different definition of borderline disease than that of Mehta et al. and randomized 21 patients to receive either gemcitabine-based chemoradiation (10 patients) or induction chemotherapy with gemcitabine, cisplatin, and 5-FU followed by radiation therapy and infusional 5-FU (11 patients). Ten ECOG institutions participated, and the study was terminated early due to poor accrual. A total of five patients underwent resection (three from the gemcitabine arm and two from the induction chemotherapy arm) with varying margin positivity in the surgical specimens. In this study, neoadjuvant strategies had acceptable toxicity profiles and resulted in comparable resectability and overall survival as other previously published regimens.

In 2008, investigators at MD Anderson Cancer Center published the first large retrospective review of neoadjuvant therapy for borderline resectable PDAC [17]. They provided an objective definition of the disease and further subdivided patients into groups A, B, and C, all as detailed above. A total of 160 histologically confirmed borderline resectable PDAC patients were identified and included for analysis over a 7-year period. Neoadjuvant therapy consisted of chemotherapy, chemoradiation, or both. Chemotherapeutic regimens included combinations of 5-FU, paclitaxel, gemcitabine, or capecitabine, and EBRT consisted of 50.4 Gy in 28 fractions or 30 Gy in 10 fractions. A total of 125 patients were restaged after completion of induction therapy and of those, 79 patients (63%) were determined to be potentially resectable and taken for exploration. Of note, the patients ineligible for operation upon restaging (43 of 125 patients) were deemed so based on not only disease progression, but also poor performance status. Poor performance status patients were thus spared an operation that is known to be considerably morbid—and the investigators in this study

reported a postoperative major complication rate of 20%, which is not insignificant. In the end, 66 of 125 restaged patients (53%) underwent a grossly complete surgical resection. Four patients had microscopically positive margins, and the remainder had an R0 resection. Median overall survival of all 160 patients was 18 months, and for the 66 resected patients was 40 months. The pathologic response to induction therapy was assessed in 63 of 66 patients, and a partial or complete response (less than 50% viable tumor remaining) was seen in 56% of patients. The authors concluded that since complete histologic responses were rarely seen, the histologic response to induction was limited to only some of the tumor, and combining this with the high rate of R0 resections implied that this pathologic partial response was significant, likely sterilizing the periphery of the tumor and facilitating the R0 resection, thus justifying a neoadjuvant approach. Additionally, patients with initially borderline resectable tumors who were able to undergo definitive surgical therapy had a real survival advantage over those with unresectable disease, highlighting a patient population who traditionally have not been offered surgery.

Other groups have conducted smaller-scale studies evaluating different neoadjuvant regimens for borderline resectable PDAC. Small et al. [77] utilized full-dose gemcitabine chemoradiation to treat 39 patients at 6 different centers, 9 of whom were borderline resectable as defined by the NCCN clinical practice guidelines. The regimen was well-tolerated, and three of the nine patients were able to be resected. A similarly sized study out of Fox Chase in 2008 [78] evaluated the treatment of 13 patients with NCCN-defined borderline resectable PDAC with both neoadjuvant chemoradiation and standalone chemotherapy, prior to surgical resection. The rationale was the potential for further tumor downstaging with the addition of standalone chemotherapy, in patients who were not clearly resectable when they were restaged. Four different radiosensitizers were used (gemcitabine, 5-FU, and capecitabine/bevacizumab), with 50.4 Gy of EBRT. The subsequent chemotherapy regimens also varied, to include combinations of gemcitabine, oxaliplatin, erlotinib, bevacizumab, and 5-FU. Negative margins were attained in 11 of 13 patients (85%). On univariate survival analysis, a tumor necrosis score of greater than 60% was associated with a statistically significant survival advantage. Although the sample size was small and the regimens varied, neoadjuvant therapy was well-tolerated and resulted in excellent margin control. Further investigation into the histopathologic response of tumor cells to neoadjuvant therapy was done by Katz et al. [83]. They identified 122 patients whose disease met borderline criteria based on the AHPBA/SSO/SSAT. These patients were treated preoperatively with either gemcitabine chemotherapy followed by gemcitabine-based chemoradiation, or chemoradiation alone. They were then restaged, and Response Evaluation Criteria In Solid Tumors (RECIST) [84] was utilized to evaluate for a reduction in tumor size or stage. Only 12% of patients (15 of 122) had a partial tumor response, but of the 85 patients that then underwent resection, 81 patients (95%) had an R0 resection. The median overall survival for resected patients was 33 months, and was not associated with a RECIST response. The authors thus concluded that a lack of RECIST response should not deter borderline patients from proceeding to surgery.

Another retrospective study was conducted by Stokes et al. [79] and included 170 patients with tissue-proven PDAC, 40 of which were borderline resectable in accordance with the MD Anderson Cancer Center classification [17]. These authors utilized capecitabine-based neoadjuvant chemoradiation. Of the 40 borderline patients, 34 completed this therapy, and upon restaging, 22 were taken for exploration and 16 were resectable. An R0 resection was attained in 12 of 16 patients (75%). The borderline resectable patients who were able to undergo neoadjuvant treatment followed by pancreatic resection had similar survival to the resectable patient population that proceeded with surgery upfront. Two separate radiation fractionation regimens were used, and the authors found a statistically significant survival benefit in the borderline resectable group that received accelerated fractionation. The conclusions reached were that the capecitabine chemoradiation strategy was feasible, safe, and effective. Stereotactic body radiation therapy (SBRT) has also been trialed with induction gemcitabine, and additionally varying combinations of gemcitabine, docetaxel, and capecitabine chemotherapy, followed by resection. In a study from H. Lee Moffitt Cancer Center [80], NCCN guidelines were used to define borderline resectable disease. Of 57 borderline patients, 32 underwent resection after completion of neoadjuvant therapy and subsequent restaging, and 96.9% (31 of 32 patients) attained an R0 resection. The only patient with an R1 resection had not completed their induction chemotherapy. SBRT, providing excellent local control with a short duration of therapy and a favorable toxicity profile, has been widely studied in locally advanced disease and is an attractive alternative to standard-course EBRT for borderline patients potentially going on to curative surgery.

As evidenced above, the trials published to date on borderline resectable PDAC have not all used the same definitions of the disease. In 2010, in an effort to more objectively define the degree of venous involvement that constitutes resectability, investigators at Fox Chase Cancer Center designed a retrospective review that utilized the Ishikawa classification of PV-SMV involvement [11, 85]. Over a 20-year period, 109 patients at this center underwent pancreatic resection for tumors involving the PV-SMV confluence. Seventy-four patients received neoadjuvant chemoradiation, while the remaining 35 underwent upfront

resection. Preoperative therapy was associated with a statistically significant increase in R0 resection, nodal basin control, and median overall survival when compared with a surgery-only approach. The patients were then stratified according to Ishikawa type, and the investigators found that patients with type II and III vein involvement (67 patients) had improved overall survival. They went on to propose that type IV and V involvement (bilateral narrowing; in this study, 42 patients) may be better classified as locally advanced disease—this, however, would need to be evaluated on a prospective basis.

The aforementioned studies all demonstrate that regardless of the regimen, neoadjuvant chemoradiation is safe and well-tolerated and can lead to improved R0 resection rates and better overall survival in the select group of patients who are appropriate candidates for this strategy. Variations in cytotoxic agents and radiation protocols, as well as the lack of a uniform definition of borderline resectable PDAC, have made it difficult to advance the care of these patients. With a widely accepted, standardized definition will come optimal staging, clinical decision making, and future clinical trials. Just recently, the Alliance for Clinical Trials in Oncology (Alliance) conducted a multicenter trial for borderline resectable PDAC patients [86], in order to evaluate the feasibility of multimodal therapy for this patient population across multiple centers experienced in their care. The primary endpoints selected were patient accrual, safety and tolerability of the preoperative regimen, and rate of pancreatectomy. This study, designed in collaboration with the Southwest Oncology Group (SWOG), Radiation Therapy Oncology Group (RTOG), and Eastern Cooperative Oncology Group (ECOG), specifically excluded resectable and locally advanced tumors by utilizing the previously published Intergroup definition of borderline resectable PDAC [20], with evaluation of imaging by a single expert radiologist. Additionally, a multidisciplinary approach was taken for overall evaluation of each patient by a medical oncologist, radiation oncologist, and a surgeon. All participating centers were required to routinely perform a minimum of 20 pancreatectomies per year, and have surgeons experienced in vascular resection and reconstruction. Twenty-two patients received at least one dose of modified FOLFIRINOX (mFOLFIRINOX- bolus oxaliplatin, irinotecan, and leucovorin, in combination with infusional 5-FU followed by pegfilgrastim), which was chosen for preoperative chemotherapy based on the survival advantage of FOLFIRINOX over gemcitabine in patients with metastatic pancreas cancer [87]. The regimen was modified by dropping the bolus 5-FU in order to partially circumvent the increased toxicity seen with FOLFIRINOX. Patients were then restaged, and if no disease progression was found, they proceeded with capecitabine-based chemoradiation followed by resection. A total of 15 patients completed all preoperative therapy and underwent resection; 12 (80%) required some form of vascular resection and reconstruction, and 93% (14 of 15 patients) had R0 resections. Adjuvant gemcitabine was administered in ten patients, and nine of those completed their adjuvant therapy. The trial met each of its primary endpoints and is the first to demonstrate that the borderline resectable PDAC can be successfully studied in a multi-institutional setting. Future studies should build on the Alliance A021101 results—specifically the standardization of diagnostic and treatment algorithms and the cooperative setting, in order to advance the care of this emerging patient population. Currently the ESPAC-5 trial is underway, which is a phase II trial comparing neoadjuvant chemotherapy (gemcitabine/capecitabine or FOLFIRINOX) versus chemoradiation for borderline resectable pancreas cancer.

Although no phase III studies have directly compared neoadjuvant therapy to a surgery-first approach, in borderline resectable disease, neoadjuvant therapy is generally recommended and is endorsed by NCCN Member Institutions.

Surgical Considerations

Surgical resection remains the definitive treatment for pancreatic ductal adenocarcinoma. As such, many aspects of the indicated operation have been evaluated to determine what effect, if any, they have on surgical morbidity and mortality, as well as oncologic outcomes. The choice of operation depends primarily upon the location of the tumor, with the vast majority of pancreatic cancers arising from the head of the pancreas and thus requiring pancreaticoduodenectomy (PD). Variations in surgical technique as well as the extent of lymphadenectomy required, the management of tumors requiring vascular resection and reconstruction, and pathologic assessment of specimens are all areas of active debate among pancreatic surgeons.

Pancreaticoduodenectomy: Historical Considerations and Surgical Technique

Allen Oldfather Whipple first published his experience with surgical treatment of ampullary carcinoma in *Annals of Surgery* in 1935 [88]. He astutely noted the morbidity of PD and advocated for a 2-stage procedure in which the first stage consisted of ligation of the common bile duct, anterior cholecystogastrostomy, and posterior gastrojejunostomy. Four to 6 weeks later, after biliary decompression and nutritional optimization, the patient returned to the operating room and underwent removal of the pancreaticoduodenal specimen, ligation of the pancreatic duct, and retroperitoneal drainage. With time, he modified the operation into 1 stage, which included an end-to-end choledochojejunostomy, end-to-side

pancreaticojejunostomy, and end-to-end gastrojejunostomy [89]. Over his career, Whipple performed a total of 37 of these operations that bear his name today.

Minor variations exist among institutions, but the standard PD remains similar to the one described by Whipple. At the University of Cincinnati, we employ a basic six steps to complete a PD [90]. A bilateral subcostal or vertical midline incision is chosen depending on body habitus, and after inspection of the liver and peritoneal surfaces for any metastatic disease, the first step is to expose the infrapancreatic superior mesenteric vein (SMV). This is done by accessing the lesser sac in the embryonic fusion plane between the greater omentum and the transverse mesocolon. The hepatic flexure is taken down and retracted out of the field. The middle colic vein is identified and followed down toward its junction with the SMV, and the visceral peritoneum is incised and the infrapancreatic SMV is exposed. Second, a wide Kocher maneuver is performed to the level of the left renal vein, which will help to facilitate eventual separation of the pancreatic head from the superior mesenteric artery (SMA). Third is the portal dissection, which begins by incising the pars lucida medially and exposing the common hepatic artery. The right gastric artery is ligated, as is the gastroduodenal artery, which allows for exposure of the portal vein below. The gallbladder is removed, the common bile duct circumferentially isolated, and the common hepatic duct is divided just above its junction with the cystic duct. The bile duct is then separated from the anterior portion of the portal vein to the level of the pancreatic neck. The stomach is transected in the fourth step, beginning at the junction of the third and fourth crossing veins on the lesser curvature, extending toward the confluence of the gastroepiploic vessels on the greater curve. Fifth, the ligament of Treitz is taken down and the jejunum transected approximately distal to the ligament of Treitz. The distal end of the specimen is flipped under the SMA/SMV, and finally in step 6, the pancreas is transected at the level of the portal vein. The specimen is separated from the SMA and SMV by ligation of small vascular tributaries to the uncinate and pancreatic head and the specimen removed. We take care to perform a periadventitial dissection along the SMA. This last step is the most critical from an oncologic perspective. Frozen sections are sent from the bile duct and pancreas margins. The retroperitoneal margin is identified for the pathologist for permanent analysis. Reconstruction begins with a retrocolic, end-to-side pancreaticojejunostomy, followed by a retrocolic end-to-side hepaticojejunostomy, and finally an antecolic gastrojejunostomy. We place a single drain at the pancreaticojejunostomy, and we do not routinely place a feeding jejunostomy or gastrostomy tubes.

Minimally invasive surgery (MIS) has been advocated by high-volume centers experienced in robotic or laparoscopic techniques. Meta-analyses examining MIS versus open pancreaticoduodenectomies have shown either nonsignificant or improved outcomes with MIS [91, 92]. However, these studies need to be interpreted with caution as many of the patients in the MIS groups were biased (smaller tumors, minimal locoregional adenopathy) compared to open. Minimally invasive pancreaticoduodenectomy should be performed only at high-volume centers experienced in these techniques, where safe and oncologically sound operations can be carried out.

Traditional Versus Pylorus-Preserving Pancreaticoduodenectomy

One area of continued debate among surgeons is whether or not to perform a standard PD or to preserve the entire stomach including the pylorus, and the very first portion of the duodenum. This pylorus-preserving PD (PPPD) was popularized by Traverso and Longmire [93, 94], with the theoretical benefit being a decreased incidence of dumping syndrome and decreased rate of marginal ulceration seen at the gastrojejunostomy in standard PD. The initial reports by Traverso and Longmire included for analysis many patients with chronic pancreatitis, and concern has since been raised about the adequacy of PPPD from an oncologic standpoint in clearing the peripyloric nodal basin. Other investigators have raised concerns about an increased incidence of delayed gastric emptying (DGE) following PPPD. Multiple studies have subsequently been performed to determine what, if any, real difference there is between PPPD and standard PD.

In 2004, Tran et al. [95] conducted a multi-institutional, prospective randomized controlled trial of 170 patients with pancreatic and periampullary tumors, with 83 patients undergoing standard PD and 87 patients undergoing PPPD. They found no differences in postoperative morbidity including DGE, mortality, rate of R0 resection, or overall survival between groups, and concluded that the two operations were equally effective. The following year, another prospective randomized controlled trial evaluating standard PD versus PPPD was done by Seiler et al. [96]. Upon subset analysis of the 110 patients with proven adenocarcinoma, 57 of whom had undergone standard PD and 53 with PPPD, the authors concluded that perioperative mortality, cumulative overall morbidity including DGE, rate of R0 resection, and lymph node positivity were the same in each group. A thorough review of all retrospective and prospective trials on standard PD versus PPPD echoes the aforementioned results [97]. Thus, with the two operations being equivalent, surgeon preference and experience should dictate which one is performed.

Extent of Lymphadenectomy

Pancreas cancer commonly first metastasizes to the lymph nodes surrounding the tumor. The standard lymphadenectomy done during pancreaticoduodenectomy includes removal of anterior and posterior pancreaticoduodenal, pyloric, bile duct, superior and inferior pancreatic head, and pancreatic body nodes. The overall poor survival of patients with PDAC has led investigators to postulate that an extended lymphadenectomy may result in better locoregional control and improved overall survival. Regional pancreatectomy, first described by Fortner in 1973 [98, 99] and popularized in Japan [100, 101], included en bloc removal of pancreatic tumor with adequate soft-tissue margin including regional lymphatic drainage, as well as the pancreatic segment of the portal vein. The extended lymphadenectomy, which has been studied of late, encompasses clearing all nodes at the hepatic hilum, along the aorta from the diaphragmatic hiatus down to the inferior mesenteric artery (IMA), laterally to both renal hila, and circumferential clearance of both the celiac axis and SMA. Pedrazzoli et al. performed the first prospective, randomized controlled trial evaluating extended lymphadenectomy during pancreaticoduodenectomy for cancer [102]. In this multicenter trial, 81 patients with potentially resectable PDAC were randomized to undergo standard ($n = 40$) or extended ($n = 41$) lymphadenectomy. Adjuvant therapy was not administered to either group. The authors found that extended lymphadenectomy did not add to postoperative morbidity, but also did not increase overall survival, which was equivalent between groups. Subgroup analysis of survival based on the presence or absence of lymph node metastases did, however, show that node-positive patients had a statistically significant survival benefit after undergoing extended lymphadenectomy ($p < 0.05$). Of note, this a posteriori analysis was not originally planned in the study design.

Investigators out of Johns Hopkins published their experience with extended lymphadenectomy during PD in a series of 299 patients with periampullary carcinoma in 2002 [103, 104]. This single-institution, prospective trial randomized 146 patients to standard and 148 to extended lymphadenectomy. The authors found a statistically significant increase in overall complication rate in the extended lymphadenectomy group (43% versus 29%, $p = 0.01$; specifically, higher rates of delayed gastric emptying and pancreatic fistula). With a median survival of 20 months in the extended group versus 21 months in the standard lymphadenectomy group, the authors concluded that extended surgical resections were not associated with increased long-term survival. The same group published an update on 5-year survival in this same cohort of patients in 2005, and again found no survival benefit to extended lymphadenectomy [105]. This sentiment was echoed by the Mayo Clinic in their prospective, randomized controlled trial of 132 patients with pancreatic head adenocarcinoma that were randomized to PD with standard (40 patients) or extended (39 patients) lymphadenectomy [106]. In this study, perioperative morbidity, mortality, and overall survival were similar between groups.

To date, there is no overtly convincing data in support of extended lymphadenectomy at the time of pancreaticoduodenectomy for PDAC. To this end, in an effort to more definitively settle the debate over these two options for nodal basin control, Pawlik et al. [107] designed and published a retrospective cohort study of 158 patients with PDAC that had undergone pancreaticoduodenectomy with removal of second-echelon lymph nodes (those along the proximal hepatic artery and/or great vessels). Their goal was to determine the actual number of patients that would be required to definitively evaluate the potential benefits of extended lymph node dissection. They devised a biostatistical model based on the following assumptions: first, that in order for extended lymphadenectomy to confer a survival benefit, an R0 resection of the primary tumor is required. Second, the only patients who would benefit from this more radical lymphadenectomy are those who would actually have positive second-tier nodes (removing negative nodes does not have a therapeutic effect). Finally, if a patient does have involved second-tier nodes, they must then have M0 disease as further lymphadenectomy will not benefit patients with visceral metastases. With this model the authors demonstrated that only 3 in 1000 patients may derive a survival benefit from extended lymphadenectomy, and further clinical trials would require a patient accrual of 202,000 into each study arm, which is a prohibitive amount. Thus, currently available data does not support the practice of extended lymphadenectomy during pancreaticoduodenectomy for pancreatic adenocarcinoma.

Vascular Resection and Reconstruction

Vascular resection and reconstruction at the time of pancreaticoduodenectomy has long been controversial, for reasons detailed by Evans et al. [108]. It adds complexity to an already challenging operation and has the potential to increase perioperative morbidity and mortality. Many surgeons have limited experience with the technical aspects of vascular surgery, and for many years, there was concern that patients requiring vascular resection had tumors with more aggressive biology and that their survival would be only marginally, if at all, improved by this high-risk operation. Lastly, the lack of a standardized pathologic evaluation of the surgical specimen across centers has resulted in poor-quality data with regard to the rate of R0 resections attained. In order for vascular resection and reconstruction to have a survival benefit, margins have to be free of cancer. Otherwise, patients incur the potential morbidity of a large operation with no survival benefit over palliative therapy.

The poor overall survival rate in resected PDAC patients has in part contributed to a search for more patients who are potentially resectable. In 1994, a series of 20 SMV/PV resections was published by Allema et al. [7], and the authors found that survival for these patients was similar to that of those who had undergone standard pancreaticoduodenectomy. They were among the first to demonstrate that not only was vascular resection feasible and safe, but that it had the potential to result in an R0 resection. Shortly thereafter, investigators out of MDACC [8] reported on their initial experience with vascular resection in 59 patients over a 3-year period who underwent traditional pancreaticoduodenectomy ($n = 36$) or pancreaticoduodenectomy with en bloc resection of the SMV/PV confluence ($n = 23$). Vascular resection patients had longer operative time, operative blood loss, and transfusion requirements, but there were no differences between groups in lymph node or margin positivity, or perioperative morbidity or mortality. The authors also advocated for the use of an interposition graft for reconstruction and recommended the internal jugular vein. Every effort was made to preserve the splenic vein to prevent sinistral hypertension, and in doing so a primary anastomosis after vein resection was more difficult and very often required interposition graft.

A larger study also out of MDACC was then published in 2004 [10] that included all 141 patients over a 13-year period who underwent pancreaticoduodenectomy requiring vascular reconstruction, and was the largest single-institution experience of vascular resection to date at the time of its publication. Patients either had tangential resection with vein patch ($n = 36$), segmental resection and primary anastomosis ($n = 35$), or segmental resection with autologous interposition graft ($n = 55$). Illustrated within their text were descriptions of the 5 types of venous resection and reconstruction performed, listed as V1 through V5. V1 involved tangential resection of the SMV/PV confluence with greater saphenous vein patch. Tumor location at the confluence requiring splenic vein ligation was either reconstructed primarily (V2) or with an interposition graft (V3). If tumor was limited to the SMV or PV and the splenic vein able to be preserved, primary reanastomosis (V4) or interposition graft (V5) was similarly utilized. These vascular resection patients were then compared with all patients over the same time frame who underwent standard pancreaticoduodenectomy, and upon analysis, vascular resection had no impact on survival duration (median survival 26.5 months for standard and 23.4 months for vascular resection). The 2-year median survival seen after venous resection far exceeds that seen in the nonoperative management of patients with the traditional definition of locally advanced, unresectable disease.

Although other retrospective studies and meta-analyses of available data have reported similar results with vascular resection [109–112], a large retrospective cohort analysis of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database that reviewed 3582 patients who underwent pancreaticoduodenectomy either with ($n = 281$) or without ($n = 3301$) vascular resection produced conflicting data [113]. This study found a statistically significant increase in 30-day postoperative morbidity (39.9% versus 33.3%) and mortality (5.7% versus 2.9%) associated with vascular resection. A possible explanation for the higher complication rates reported in this study is detailed by Tseng [114], because the Current Procedural Terminology (CPT) codes utilized for data analysis included operations with inadvertent vascular injury requiring repair. When a surgeon encounters unexpected vascular involvement during pancreaticoduodenectomy, the operation often results in either vascular injury with significant blood loss and subsequent vascular repair upon proceeding with attempted R0 resection, or a grossly positive resection (R2) margin to avoid potential operative catastrophe. This further illustrates the necessity of both thorough preoperative planning and the surgical technical expertise required to safely complete these operations. Appropriate patient selection and care at high-volume centers is essential.

Conclusion

Pancreas cancer remains a disease with dismal survival. The American Cancer Society estimates that it will take the lives of approximately 40,000 patients in 2015. Evolving knowledge that PDAC is likely a systemic disease at the time of diagnosis has prompted the call for not only better multimodal therapy, but also the search for improved diagnostics that would theoretically result in earlier diagnosis and better prognosis. Continued progress in terms of overall survival will require advancements in chemotherapeutic and radiation strategies as well as evolving targeted agents as our understanding of the biology of pancreas cancer broadens. Essential now is the accurate staging of PDAC patients. Improvements in both high-resolution imaging as well as surgical technique have brought focus onto the borderline resectable patient population. Evolving data indicate that these patients, when diagnosed, staged, and treated in a multidisciplinary setting and with a multimodality approach, can achieve significant disease-free and long-term survival. It is more and more evident that comprehensive management of pancreas cancer is best done in high-volume centers where medical oncologists, radiologists, and surgeons skilled in complex pancreatic surgery all collaborate on a daily basis. Standardization of diagnostic and treatment algorithms across centers will facilitate large-scale clinical trials and accrue more data, helping to improve the long-term survival of patients with pancreas cancer.

References

1. Anonymous. Seer cancer statistics-pancreas, 2007–2013. [cited 2018]; Available from: https://seer.cancer.gov/statfacts/html/pancreas.html.
2. Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. Cancer. 1993;72(7):2118–23.
3. Griffin JF, Smalley SR, Jewell W, Paradelo JC, Reymond RD, Hassanein RE, et al. Patterns of failure after curative resection of pancreatic carcinoma. Cancer. 1990;66(1):56–61.
4. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1727–33.
5. Evans DB, Multidisciplinary Pancreatic Cancer Study G. Resectable pancreatic cancer: the role for neoadjuvant/preoperative therapy. HPB (Oxford). 2006;8(5):365–8.
6. O'Malley ME, Boland GW, Wood BJ, Fernandez-del Castillo C, Warshaw AL, Mueller PR. Adenocarcinoma of the head of the pancreas: determination of surgical unresectability with thin-section pancreatic-phase helical ct. AJR Am J Roentgenol. 1999;173(6):1513–8.
7. Allema JH, Reinders ME, van Gulik TM, van Leeuwen DJ, de Wit LT, Verbeek PC, et al. Portal vein resection in patients undergoing pancreatoduodenectomy for carcinoma of the pancreatic head. Br J Surg. 1994;81(11):1642–6.
8. Fuhrman GM, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, et al. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic tumor study group. Ann Surg. 1996;223(2):154–62.
9. Leach SD, Lee JE, Charnsangavej C, Cleary KR, Lowy AM, Fenoglio CJ, et al. Survival following pancreaticoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. Br J Surg. 1998;85(5):611–7.
10. Tseng JF, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg. 2004;8(8):935–49; discussion 949–950.
11. Ishikawa O, Ohigashi H, Imaoka S, Furukawa H, Sasaki Y, Fujita M, et al. Preoperative indications for extended pancreatectomy for locally advanced pancreas cancer involving the portal vein. Ann Surg. 1992;215(3):231–6.
12. Loyer EM, David CL, Dubrow RA, Evans DB, Charnsangavej C. Vascular involvement in pancreatic adenocarcinoma: reassessment by thin-section ct. Abdom Imaging. 1996;21(3):202–6.
13. Lu DS, Reber HA, Krasny RM, Kadell BM, Sayre J. Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical ct. AJR Am J Roentgenol. 1997;168(6):1439–43.
14. Tran Cao HS, Balachandran A, Wang H, Nogueras-Gonzalez GM, Bailey CE, Lee JE, et al. Radiographic tumor-vein interface as a predictor of intraoperative, pathologic, and oncologic outcomes in resectable and borderline resectable pancreatic cancer. J Gastrointest Surg. 2014;18(2):269–78; discussion 278.
15. Network NCC. National comprehensive cancer network (nccn) clinical practice guidelines in oncology. Pancreatic adenocarcinoma. Available from: http://www.nccn.org/professionals/physician_gls/default.asp.
16. Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol. 2006;13(8):1035–46.
17. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008;206(5):833–46; discussion 846-838.
18. Katz MH, Pisters PW, Lee JE, Fleming JB. Borderline resectable pancreatic cancer: what have we learned and where do we go from here? Ann Surg Oncol. 2011;18(3):608–10.
19. Kelly KJ, Winslow E, Kooby D, Lad NL, Parikh AA, Scoggins CR, et al. Vein involvement during pancreaticoduodenectomy: is there a need for redefinition of "borderline resectable disease"? J Gastrointest Surg. 2013;17(7):1209–17; discussion 1217.
20. Katz MH, Marsh R, Herman JM, Shi Q, Collison E, Venook AP, et al. Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. Ann Surg Oncol. 2013;20(8):2787–95.
21. Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. Clin Gastroenterol Hepatol. 2008;6(12):1301–8.
22. Megibow AJ, Babb JS, Hecht EM, Cho JJ, Houston C, Boruch MM, et al. Evaluation of bowel distention and bowel wall appearance by using neutral oral contrast agent for multi-detector row ct. Radiology. 2006;238(1):87–95.
23. Bronstein YL, Loyer EM, Kaur H, Choi H, David C, DuBrow RA, et al. Detection of small pancreatic tumors with multiphasic helical ct. AJR Am J Roentgenol. 2004;182(3):619–23.
24. White R, Winston C, Gonen M, D'Angelica M, Jarnagin W, Fong Y, et al. Current utility of staging laparoscopy for pancreatic and peripancreatic neoplasms. J Am Coll Surg. 2008;206(3):445–50.
25. Borbath I, Van Beers BE, Lonneux M, Schoonbroodt D, Geubel A, Gigot JF, et al. Preoperative assessment of pancreatic tumors using magnetic resonance imaging, endoscopic ultrasonography, positron emission tomography and laparoscopy. Pancreatology. 2005;5(6):553–61.
26. Friess H, Kleeff J, Silva JC, Sadowski C, Baer HU, Buchler MW. The role of diagnostic laparoscopy in pancreatic and periampullary malignancies. J Am Coll Surg. 1998;186(6):675–82.
27. Walters DM, Lapar DJ, de Lange EE, Sarti M, Stokes JB, Adams RB, et al. Pancreas-protocol imaging at a high-volume center leads to improved preoperative staging of pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2011;18(10):2764–71.
28. Porembka MR, Hawkins WG, Linehan DC, Gao F, Ma C, Brunt EM, et al. Radiologic and intraoperative detection of need for mesenteric vein resection in patients with adenocarcinoma of the head of the pancreas. HPB (Oxford). 2011;13(9):633–42.
29. Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg. 2007;246(1):52–60.
30. Halligan S. Subspecialist radiology. Clin Radiol. 2002;57(11):982–3.
31. Muller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic us, ct, and mr imaging. Radiology. 1994;190(3):745–51.
32. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass?: a meta-analysis and systematic review. Pancreas. 2013;42(1):20–6.
33. Adler DG, Jacobson BC, Davila RE, Hirota WK, Leighton JA, Qureshi WA, et al. Asge guideline: complications of eus. Gastrointest Endosc. 2005;61(1):8–12.
34. Lee ES. Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. World J Gastroenterol. 2014;20(24):7864–77.
35. Raman SP, Horton KM, Fishman EK. Multimodality imaging of pancreatic cancer-computed tomography, magnetic resonance imaging, and positron emission tomography. Cancer J. 2012;18(6):511–22.
36. Miller FH, Rini NJ, Keppke AL. Mri of adenocarcinoma of the pancreas. AJR Am J Roentgenol. 2006;187(4):W365–74.

37. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267–77.
38. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725–30.
39. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. 1991;324(11):709–15.
40. Moertel CG, Childs DS Jr, Reitemeier RJ, Colby MY Jr, Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet. 1969;2(7626):865–7.
41. Haslam JB, Cavanaugh PJ, Stroup SL. Radiation therapy in the treatment of irresectable adenocarcinoma of the pancreas. Cancer. 1973;32(6):1341–5.
42. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120(8):899–903.
43. Anonymous. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal tumor study group. Cancer. 1987;59(12):2006–10.
44. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase iii trial of the eortc gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776–82; discussion 782-774.
45. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200–10.
46. 3rd Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403–13.
47. Neuhaus P, Riess H, Post S, Gellert K, Ridwelski K, Schramm H, Zuelke C, Fahlke J, Langrehr J, Oettle H. Oettle Deutsche Krebsgesellschaft (CAO/AIO) Conko-001: final results of the randomized, prospective, multicenter phase iii trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer (pc). J Clin Oncol. 2008;26(15S):LBA 4504.
48. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299(9):1019–26.
49. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073–81.
50. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (espac-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24.
51. Lawrence TS, Davis MA, Hough A, Rehemtulla A. The role of apoptosis in 2',2'-difluoro-2'-deoxycytidine (gemcitabine)-mediated radiosensitization. Clin Cancer Res. 2001;7(2):314–9.
52. Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized eortc-40013-22012/ffcd-9203/gercor phase ii study. J Clin Oncol. 2010;28(29):4450–6.
53. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of s-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (jaspac 01). Lancet. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2016;388(10041):248–57.
54. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase iii trial of the national cancer institute of canada clinical trials group. J Clin Oncol. 2007;25(15):1960–6.
55. Van Cutsem E, van de Velde H, Karasek P, Oettle H, Vervenne WL, Szawlowski A, et al. Phase iii trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol. 2004;22(8):1430–8.
56. Yeo CJ, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg. 1997;225(5):621–33; discussion 633-626.
57. Spitz FR, Abbruzzese JL, Lee JE, Pisters PW, Lowy AM, Fenoglio CJ, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol. 1997;15(3):928–37.
58. Cheng TY, Sheth K, White RR, Ueno T, Hung CF, Clary BM, et al. Effect of neoadjuvant chemoradiation on operative mortality and morbidity for pancreaticoduodenectomy. Ann Surg Oncol. 2006;13(1):66–74.
59. Lowy AM, Lee JE, Pisters PW, Davidson BS, Fenoglio CJ, Stanford P, et al. Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. Ann Surg. 1997;226(5):632–41.
60. Hoffman JP, Lipsitz S, Pisansky T, Weese JL, Solin L, Benson AB 3rd. Phase ii trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an eastern cooperative oncology group study. J Clin Oncol. 1998;16(1):317–23.
61. Pisters PW, Hudec WA, Lee JE, Raijman I, Lahoti S, Janjan NA, et al. Preoperative chemoradiation for patients with pancreatic cancer: toxicity of endobiliary stents. J Clin Oncol. 2000;18(4):860–7.
62. White RR, Hurwitz HI, Morse MA, Lee C, Anscher MS, Paulson EK, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. Ann Surg Oncol. 2001;8(10):758–65.
63. Tzeng CW, Tran Cao HS, Lee JE, Pisters PW, Varadhachary GR, Wolff RA, et al. Treatment sequencing for resectable pancreatic cancer: influence of early metastases and surgical complications on multimodality therapy completion and survival. J Gastrointest Surg. 2014;18(1):16–24; discussion 24-15.
64. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg. 1992;127(11):1335–9.
65. Pisters PW, Abbruzzese JL, Janjan NA, Cleary KR, Charnsangavej C, Goswitz MS, et al. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. J Clin Oncol. 1998;16(12):3843–50.
66. Yeung RS, Weese JL, Hoffman JP, Solin LJ, Paul AR, Engstrom PF, et al. Neoadjuvant chemoradiation in pancreatic and duodenal carcinoma. A phase ii study. Cancer. 1993;72(7):2124–33.
67. Talamonti MS, Jr Small W, Mulcahy MF, Wayne JD, Attaluri V, Colletti LM, et al. A multi-institutional phase ii trial of preoperative full-dose gemcitabine and concurrent radiation for patients

with potentially resectable pancreatic carcinoma. Ann Surg Oncol. 2006;13(2):150–8.
68. Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26(21):3496–502.
69. Philip PA, Zalupski MM, Vaitkevicius VK, Arlauskas P, Chaplen R, Heilbrun LK, et al. Phase ii study of gemcitabine and cisplatin in the treatment of patients with advanced pancreatic carcinoma. Cancer. 2001;92(3):569–77.
70. Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26(21):3487–95.
71. Kim EJ, Ben-Josef E, Herman JM, Bekaii-Saab T, Dawson LA, Griffith KA, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. Cancer. 2013;119(15):2692–700.
72. Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Ann Surg Oncol. 2007;14(7):2088–96.
73. Heinrich S, Schafer M, Weber A, Hany TF, Bhure U, Pestalozzi BC, et al. Neoadjuvant chemotherapy generates a significant tumor response in resectable pancreatic cancer without increasing morbidity: results of a prospective phase ii trial. Ann Surg. 2008;248(6):1014–22.
74. Heinrich S, Pestalozzi BC, Schafer M, Weber A, Bauerfeind P, Knuth A, et al. Prospective phase ii trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26(15):2526–31.
75. O'Reilly EM, Perelshteyn A, Jarnagin WR, Schattner M, Gerdes H, Capanu M, et al. A single-arm, nonrandomized phase ii trial of neoadjuvant gemcitabine and oxaliplatin in patients with resectable pancreas adenocarcinoma. Ann Surg. 2014;260(1):142–8.
76. Mehta VK, Fisher G, Ford JA, Poen JC, Vierra MA, Oberhelman H, et al. Preoperative chemoradiation for marginally resectable adenocarcinoma of the pancreas. J Gastrointest Surg. 2001;5(1):27–35.
77. Jr Small W, Berlin J, Freedman GM, Lawrence T, Talamonti MS, Mulcahy MF, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase ii trial. J Clin Oncol. 2008;26(6):942–7.
78. Brown KM, Siripurapu V, Davidson M, Cohen SJ, Konski A, Watson JC, et al. Chemoradiation followed by chemotherapy before resection for borderline pancreatic adenocarcinoma. Am J Surg. 2008;195(3):318–21.
79. Stokes JB, Nolan NJ, Stelow EB, Walters DM, Weiss GR, de Lange EE, et al. Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. Ann Surg Oncol. 2011;18(3):619–27.
80. Chuong MD, Springett GM, Freilich JM, Park CK, Weber JM, Mellon EA, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys. 2013;86(3):516–22.
81. Abrams RA, Lowy AM, O'Reilly EM, Wolff RA, Picozzi VJ, Pisters PW. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1751–6.
82. Landry J, Catalano PJ, Staley C, Harris W, Hoffman J, Talamonti M, et al. Randomized phase ii study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. J Surg Oncol. 2010;101(7):587–92.
83. Katz MH, Fleming JB, Bhosale P, Varadhachary G, Lee JE, Wolff R, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer. 2012;118(23):5749–56.
84. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised recist guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
85. Chun YS, Milestone BN, Watson JC, Cohen SJ, Burtness B, Engstrom PF, et al. Defining venous involvement in borderline resectable pancreatic cancer. Ann Surg Oncol. 2010;17(11):2832–8.
86. Katz MHG, QS SAA, Herman JM, Marsh R d W, Collisson EA, Schwartz LH, Martin RCG, Conway WC, Truty M, Kindler HL, Lowy AM, Philip PA, Bekaii-Saab TS, Cardin DB, LoConte NK, Venook AP. Preoperative modified folfirinox (mfolfirinox) followed by chemoradiation (crt) for borderline resectable (blr) pancreatic cancer (pdac): initial results from alliance trial a021101. J Clin Oncol, ASCO Annual Meeting. 2015;33(15, May 20 Supplement):4008.
87. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
88. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of vater. Ann Surg. 1935;102(4):763–79.
89. Whipple AO. Observations on radical surgery for lesions of the pancreas. Surg Gynecol Obstet. 1946;82:623–31.
90. Ahmad SA, Lowy AM, McIntyre BC, Matthews JB. Pancreaticoduodenectomy. J Gastrointest Surg. 2005;9(1):138–43.
91. de Rooij T, Lu MZ, Steen MW, Gerhards MF, Dijkgraaf MG, Busch OR, et al. Minimally invasive versus open pancreatoduodenectomy: systematic review and meta-analysis of comparative cohort and registry studies. Ann Surg. 2016;264(2):257–67.
92. Correa-Gallego C, Dinkelspiel HE, Sulimanoff I, Fisher S, Vinuela EF, Kingham TP, et al. Minimally-invasive vs open pancreaticoduodenectomy: systematic review and meta-analysis. J Am Coll Surg. 2014;218(1):129–39.
93. Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet. 1978;146(6):959–62.
94. Traverso LW, Jr Longmire WP. Preservation of the pylorus in pancreaticoduodenectomy a follow-up evaluation. Ann Surg. 1980;192(3):306–10.
95. Tran KT, Smeenk HG, van Eijck CH, Kazemier G, Hop WC, Greve JW, et al. Pylorus preserving pancreaticoduodenectomy versus standard whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. Ann Surg. 2004;240(5):738–45.
96. Seiler CA, Wagner M, Bachmann T, Redaelli CA, Schmied B, Uhl W, et al. Randomized clinical trial of pylorus-preserving duodenopancreatectomy versus classical whipple resection-long term results. Br J Surg. 2005;92(5):547–56.
97. Diener MK, Heukaufer C, Schwarzer G, Seiler CM, Antes G, Buchler M, et al. Pancreaticoduodenectomy (classic whipple) versus pylorus-preserving pancreaticoduodenectomy (pp whipple) for surgical treatment of periampullary and pancreatic carcinoma. Cochrane Database Syst Rev. 2008;(2):Cd006053.
98. Fortner JG. Regional resection of cancer of the pancreas: a new surgical approach. Surgery. 1973;73(2):307–20.
99. Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Tumor staging and results. Ann Surg. 1984;199(4):418–25.
100. Ishikawa O, Ohhigashi H, Sasaki Y, Kabuto T, Fukuda I, Furukawa H, et al. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. Ann Surg. 1988;208(2):215–20.

101. Manabe T, Ohshio G, Baba N, Miyashita T, Asano N, Tamura K, et al. Radical pancreatectomy for ductal cell carcinoma of the head of the pancreas. Cancer. 1989;64(5):1132–7.
102. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy study group. Ann Surg. 1998;228(4):508–17.
103. Yeo CJ, Cameron JL, Sohn TA, Coleman J, Sauter PK, Hruban RH, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg. 1999;229(5):613–22; discussion 622-614.
104. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002;236(3):355–66; discussion 366-358.
105. Riall TS, Cameron JL, Lillemoe KD, Campbell KA, Sauter PK, Coleman J, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma--part 3: Update on 5-year survival. J Gastrointest Surg. 2005;9(9):1191–204; discussion 1204-1196.
106. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 2005;138(4):618–28; discussion 628-630.
107. Pawlik TM, Abdalla EK, Barnett CC, Ahmad SA, Cleary KR, Vauthey JN, et al. Feasibility of a randomized trial of extended lymphadenectomy for pancreatic cancer. Arch Surg. 2005;140(6):584–9; discussion 589-591.
108. Evans DB, Farnell MB, Lillemoe KD, Jr Vollmer C, Strasberg SM, Schulick RD. Surgical treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1736–44.
109. Ravikumar R, Sabin C, Abu Hilal M, Bramhall S, White S, Wigmore S, et al. Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study. J Am Coll Surg. 2014;218(3):401–11.
110. Zhou Y, Zhang Z, Liu Y, Li B, Xu D. Pancreatectomy combined with superior mesenteric vein-portal vein resection for pancreatic cancer: a meta-analysis. World J Surg. 2012;36(4):884–91.
111. Chua TC, Saxena A. Extended pancreaticoduodenectomy with vascular resection for pancreatic cancer: a systematic review. J Gastrointest Surg. 2010;14(9):1442–52.
112. Liles JS, Katz MH. Pancreaticoduodenectomy with vascular resection for pancreatic head adenocarcinoma. Expert Rev Anticancer Ther. 2014;14(8):919–29.
113. Castleberry AW, White RR, De La Fuente SG, Clary BM, 3rd Blazer DG, McCann RL, et al. The impact of vascular resection on early postoperative outcomes after pancreaticoduodenectomy: an analysis of the american college of surgeons national surgical quality improvement program database. Ann Surg Oncol. 2012;19(13):4068–77.
114. Tseng JF. Proceed with caution: vascular resection at pancreaticoduodenectomy. Ann Surg Oncol. 2012;19(13):4001–2.

Treatment of Advanced Pancreatic Carcinoma

15

Anteneh Tesfaye and Philip A. Philip

Background

More than 85% of pancreatic cancer is pancreatic ductal adenocarcinoma; the rest is comprised of rare histologic forms such as neuroendocrine tumor and other less common histologic variants. It is estimated that pancreatic cancer will likely become the second leading cause of cancer-related death in the United States by 2020 [1]. A total of 53,070 people were expected to be diagnosed with pancreatic cancer in the United States in 2016, and 41,780 were estimated to die of the disease, making it the fourth most deadly malignancy currently [2]. More than 75% of patients die within a year of diagnosis. In addition to the aggressive biology, lack of effective treatments is a major reason why a cancer that ranks 12th in incidence ranks so high in cancer-related mortality.

Although the precise etiologic factors are still not well understood, the most frequently cited risk factors include cigarette smoking, chronic pancreatitis, diabetes mellitus, and obesity [3–6]. More than 90% of cases of pancreatic adenocarcinoma are sporadic in nature. Only a minority of patients have identifiable familial genetic predispositions such as *BRCA1/2* and *PALB2* mutations, hereditary pancreatitis, Lynch syndrome, and Peutz-Jeghers syndrome [7–11].

Surgical resection of pancreas cancer remains the only treatment modality with a potential for cure. However, less than 20% of patients with pancreatic adenocarcinoma present with surgically operable tumors. Nearly half of the patients have clinical or radiographic evidence of metastatic disease upon initial presentation. Hence, many patients with pancreatic adenocarcinoma present with an incurable disease. The 5-year survival rate for patients with pancreatic adenocarcinoma is estimated to be less than 5% [1].

Metastatic pancreas adenocarcinoma, unlike other chemotherapy-sensitive metastatic cancers, is very resistant to treatment, and an aggressive clinical course is one of its hallmarks. Modern cancer chemotherapy has shown only modest improvement in the outcome of patients with pancreas cancer. These outcomes fall significantly short of patients' and physicians' expectations unlike other malignancies where therapeutic breakthrough has led to significant improvement in outcomes. The median overall survival of patients with metastatic adenocarcinoma treated with newer regimens has improved to 8.5–11 months with modern-day chemotherapy compared to the historical benchmark of 5–6 months [12, 13]. With the incorporation of second-line therapy, an increasing number of patients live more than a year [14].

Although statistically significant improvement has been achieved in the survival outcomes of these patients, the overall survival benefit is very small relative to what has been achieved in other malignancies. Hence, innovative approaches to treat pancreatic cancer are desperately needed. This must be based on better understanding of the biology of the disease that would help design better therapies.

The other major challenge in treating patients with pancreatic cancer is lack of reliable biomarkers to guide patient selection for a specific treatment strategy. Many clinical trials that have evaluated newer treatment strategies have shown only very modest benefits or have been flat out negative. In this chapter, we discuss available treatments and explore newer therapeutic approaches being evaluated in metastatic pancreatic adenocarcinoma.

A. Tesfaye (✉)
Department of Oncology, Karmanos Cancer Institute, Detroit, MI, USA
e-mail: tesfayea@karmanos.org

P. A. Philip
Department of Oncology, Department of Pharmacology, Wayne State University, Karmanos Cancer Institute, Hudson-Webber Cancer Research Center, Detroit, MI, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_15

Current Chemotherapy Regimens for Advanced Pancreatic Cancer

Frontline

To this day, chemotherapy remains the cornerstone of the treatment for metastatic pancreatic adenocarcinoma. However, chemotherapy produces very modest improvement in overall survival and quality of life of patients with advanced pancreatic cancer. There are four regimens that have been approved by the US Food and Drug Administration (FDA) in the frontline setting for patients with metastatic pancreatic adenocarcinoma (Table 15.1) [12, 13, 15–17].

Gemcitabine

In a phase III study of gemcitabine versus intravenous bolus administration of 5-fluorouracil (5-FU), a very modest improvement in progression-free survival (PFS) and overall survival (OS) was seen [15]. The improvement in the median overall survival was 5.7 months, compared with 4.4 months in the control (P = 0.0025). The FDA approval of gemcitabine was mainly because the study met its primary endpoint of improving quality of life scores when compared to 5-FU alone.

Gemcitabine and Erlotinib

Erlotinib is an oral epidermal growth factor receptor (EGFR)-related tyrosine kinase inhibitor. Moore et al. demonstrated a marginal and clinically very questionable benefit for the combination of gemcitabine and erlotinib in patients with metastatic or locally advanced unresectable pancreatic cancer. The study involved subjects who were not molecularly selected. The study showed improvement in median progression-free survival (3.75 vs 3.55 months; P = 0.004) and median overall survival (6.24 vs 5.91 months; P = 0.038) when compared with single-agent gemcitabine [16]. Although statistically significant, the difference in the survival outcome is considered as clinically insignificant, especially at the expense of added drug toxicity and cost. Hence, this combination is rarely used nowadays.

FOLFIRINOX (5-FU, Leucovorin, Oxaliplatin, and Irinotecan)

The French study by Conroy et al. randomized 342 patients with metastatic pancreatic cancer to receive FOLFIRINOX (5-FU, leucovorin, oxaliplatin, and irinotecan) given every 2 weeks vs single-agent standard-dose gemcitabine [12]. The patients treated with FOLFIRINOX had significantly improved median overall survival (11.1 months vs 6.6 months, $P < 0.001$). The median progression-free survival was also significantly improved to 6.4 months vs 3.3 months ($P < 0.001$). However, there were increased chemotherapy-related toxicities (i.e., neutropenia, febrile neutropenia, thrombocytopenia, alanine aminotransferase elevation, diarrhea, and neuropathy) seen among the patients in the combination arm. The study is sometimes criticized as all the patients were French, younger (median age 61 and maximum age 75), and had a very good performance status (PS)—38% had an Eastern Cooperative Oncology Group (ECOG) PS of 0, and 62% had an ECOG PS of 1. Despite the higher incidence of side effects, the patients in the combination arm enjoyed better quality of life on objective assessment at 6 months. As this regimen is composed of 3 chemotherapeutic drugs, using it as a backbone for further clinical trial design has been difficult due to significantly increased toxicity to patients. In common practice, a modified version of this regimen is used, and the most common alteration is the omission of the bolus 5-FU. Most oncologists would prefer the addition of hematopoietic colony growth factors to mitigate neutropenic fever and treatment delays.

Table 15.1 US Food and Drug Administration-approved first-line and second-line treatment options [12, 13, 15–17]

References	Sample size	Regimens	Response rate	PFS (mon)	OS (mon)
First-line therapies					
Conroy et al. [12]	342	FOLFIRINOX	32.0	6.4	11.1
		Gemcitabine	9.4	3.3	6.8
von Hoff et al. [13]	861	Nab-paclitaxel + gemcitabine	23.0	5.5	8.5
		Gemcitabine	7.0	3.7	6.7
Moore et al. [16]	569	Gemcitabine + erlotinib	8.6	3.75	6.24
		Gemcitabine	8.0	3.55	5.91
Burris et al. [15]	126	Gemcitabine	5.4	3.7	5.65
		5-FU	0	1.6	4.41
Second-line therapies					
Wang-Gillam et al. [17]	417	Nanoliposomal irinotecan	6	2.7	4.9
		Nanoliposomal irinotecan +5-FU	16	3.1	6.1
		5-FU	1	1.6	4.2

5-FU 5-fluorouracil

Gemcitabine and Nab-Paclitaxel

Von Hoff et al. showed that gemcitabine with nab-paclitaxel had better median PFS (5.5 vs 3.7 months; $P < 0.001$) and median OS (8.5 vs 7.6 months; $P < 0.001$) in metastatic pancreatic adenocarcinoma compared with gemcitabine alone (MPACT trial) [13]. Unlike the FOLFIRINOX study, this was an international trial of 861 patients that included patients with ECOG performance status of 2. The gemcitabine and nab-paclitaxel regimen was generally well tolerated, the main adverse events being febrile neutropenia and peripheral neuropathy. As this regimen has fewer chemotherapy drugs and is well tolerated, it has been used in many ongoing studies testing new molecules in clinical trials of metastatic pancreatic adenocarcinoma.

Second-Line Systemic Therapies for Advanced Pancreatic Cancer

Treatment for metastatic pancreatic adenocarcinoma in the second-line setting has been less well defined because many patients are unable to receive second-line therapy or be enrolled in such clinical trials (Table 15.1) [17]. Many clinicians are wary of the merits of treatment beyond the frontline setting in metastatic pancreatic adenocarcinoma. Although many studies have shown some clinical benefit in second-line treatments, the response rate to chemotherapy and the magnitude of benefit is generally much lower compared to frontline regimens.

Chiorean et al. analyzed the outcomes of second-line therapy in patients with metastatic pancreatic adenocarcinoma in the MPACT trial upon disease progression after either nab-paclitaxel plus gemcitabine or after gemcitabine. Most patients received a second-line treatment containing a fluoropyrimidine (267 out of 347, 77%). They found that the median total survival for patients with a fluoropyrimidine-containing second-line therapy after nab-paclitaxel and gemcitabine vs gemcitabine was 13.5 vs 9.5 months ($P = 0.012$). The study showed that receiving a second-line therapy was one of the independent factors associated with longer survival post first-line therapy in these patients [14].

Nanoliposomal Irinotecan and 5-FU

Nanoliposomal encapsulated irinotecan (MM-398) is a novel chemotherapy formulation of irinotecan that is approved for treatment of metastatic pancreatic adenocarcinoma in the second-line setting. The phase III NAPOLI trial showed that in patients with metastatic pancreatic cancer who were previously treated with gemcitabine-based therapy, a combination of MM-398 and 5-FU showed modest improvement in the median overall survival (6.1 months) compared to single-agent 5-FU/leucovorin (4.2 months; $P = 0.012$), while there was no difference between single-agent MM-398 and single-agent 5-FU/leucovorin. Fatigue, neutropenia, diarrhea, and vomiting were the main grade 3 adverse events seen in higher frequency in the combination arm [17]. It is not known whether MM-398 offers any benefit over standard irinotecan in these patient population because the study did not include a comparison with standard irinotecan and 5-FU (FOLFIRI) combination.

Oxaliplatin, Folinic Acid, and 5-Fluorouracil (OFF)

The German CONKO-003 trial investigated the role of OFF (oxaliplatin, folinic acid, and 5-fluorouracil) versus single-agent folinic acid and 5-fluorouracil (FF) in a phase III trial for patients with pancreatic cancer who received prior gemcitabine-based chemotherapy. Although this regimen contains all the drugs in the FOLFOX regimen, the administration and scheduling is different. Median follow-up was 54.1 months, and 160 patients were eligible for the primary analysis. The median overall survival in the OFF group (5.9 months) was modestly improved compared to the FF group (3.3 months, $p < 0.01$). There was also improvement in time to progression in the OFF arm. Except for higher rates of grades 1–2 neurotoxicity in the OFF arm, adverse events were comparable between the 2 arms [18].

FOLFOX (5-Fluorouracil, Folinic Acid, and Oxaliplatin)

The FOLFOX regimen is commonly used in the frontline setting in patients with advanced colorectal and gastroesophageal cancers. As second-line treatment in patients with metastatic pancreatic adenocarcinoma, response rates have been 0–23% with overall survivals from 3.5 to 6 months [19–24]. A single-arm phase II study of FOLFOX 4 in patients with metastatic pancreatic adenocarcinoma after failure of gemcitabine-based frontline therapy showed a median time to progression of 9.9 weeks, and the median overall survival was 31.1 weeks [25]. Gill et al. conducted a randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy (PANCREOX). The study did not show any benefit in the combination arm over single-agent infusional 5-FU. In fact, the single-agent arm had better overall survival as more patients were able to receive a third-line treatment after disease progression, unlike the patients in the mFOLFOX arm [26].

Gemcitabine and Nab-Paclitaxel

Portal et al. reviewed outcomes of patients with metastatic pancreatic adenocarcinoma who received gemcitabine nab-paclitaxel in the second-line setting after disease progression with the FOLFIRINOX regimen in a prospective observational study. Treatment with gemcitabine nab-paclitaxel was per the MPACT trial. Although it is an observational study

with a small sample size (57), the disease control rate was 58%, with a 17.5% objective response rate. Median overall survival was 8.8 months (95% CI, 6.2–9.7), and median progression-free survival was 5.1 months (95% CI, 3.2–6.2) [27]. Currently, there are ongoing prospective studies evaluating the role of this regimen in the second-line setting for this patient population.

5-Fluorouracil and Irinotecan (FOLFIRI)

The 5-fluorouracil and irinotecan doublet (FOLFIRI) regimen, or its variations, has been shown by different studies to have activity in the second-line setting. The median overall survival observed is around 4–6 months in the second-line setting [20, 28, 29].

Targeted Therapies

Targeting a mutated gene seems to be a logical approach, and many in the field have been motivated to develop targeted therapeutic approaches, learning from experience in cancers such as chronic myelogenous leukemia where a tyrosine kinase inhibitor revolutionized the care of the once deadly disease. However, in pancreatic cancer treatment, targeting a single genetic alteration or pathway has met with little, if any, success. There are a number of explanations as to why targeted therapy has been ineffective in pancreatic adenocarcinoma and other solid tumors. The vast majority of pancreatic cancers have mutations in the *KRAS* gene that are currently not targetable. There are also very frequent mutations in tumor suppressor genes—such as the *p53*, *p16*, and *SMAD4*—that are not amenable to targeted therapies. Moreover, the molecular makeup of tumors is heterogeneous and may be misrepresented when a tumor deposit is sampled by a fine needle for diagnostic purposes. It is also recognized that as tumors progress, their genetic makeup will also change [30]. Cancer cells have redundant intracellular signaling pathways. A molecule that is being targeted with an appropriately matched agent may not be critical for the survival of the cell. The redundant pathways along with cross-talk between pathways may act as an escape or drug resistance mechanism when attempting to block signaling pathways.

We will discuss a few of the pathways that have been explored in targeted treatments.

Growth Factors and Growth Factor Receptors

RAS

Oncogenic *KRAS* mutation is an important genetic event in the oncogenesis and progression of pancreatic adenocarcinoma (Fig. 15.1) [31, 32]. This activating mutation is believed to occur very early in carcinogenesis [33, 34]. Oncogenic *KRAS* plays a critical metabolic role in the tumor-like stimulation of glucose uptake and its intracellular transport, amino acid metabolism, increased autophagy, and subsequent recycling of organelles leading to uncontrolled proliferation of pancreatic adenocarcinoma cells. This mutation is seen in approximately 95% of pancreatic ductal adenocarcinoma [34, 35]. Because of its high prevalence and critical role in oncogenesis, *KRAS* mutation has been a target of high interest for drug development. However, finding a therapeutic intervention that targets this mutation has been elusive over the last few decades [34]. So far there is no therapeutic intervention that can target the activated *KRAS* mutation. Investigators attempted to block pathways downstream of RAS in an attempt to control RAS-mediated signaling. Chung et al. conducted a randomized prospective trial to compare mFOLFOX with dual targeting of the MEK and PI3K/AKT pathways downstream of KRAS by selumetinib plus MK-2206 in patients with metastatic pancreatic adenocarcinoma for whom gemcitabine-based chemotherapy had failed. The dual inhibition of MEK and PI3K/AKT pathways did not improve overall survival of these patients [36].

EGFR, IGF-1R, Her-2, and Downstream Molecules

The addition of the tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), erlotinib, to gemcitabine showed a marginal clinical benefit in patients with advanced pancreatic adenocarcinoma as discussed earlier [16]. However, the Southwest Oncology Group (SWOG) phase III S-0205 trial comparing the combination of gemcitabine and cetuximab (monoclonal antibody against EGFR) versus gemcitabine alone in patients with advanced pancreatic adenocarcinoma did not show any benefit from the addition of cetuximab to gemcitabine. A majority (90%) of the patients had tumoral EGFR expression, but there was no treatment benefit in this subset of patients [37]. The role of blocking insulin-like growth factor receptor-1 (IGF-1R) along with epidermal growth factor receptor and gemcitabine was studied in the SWOG 0727. The combination of cixutumumab (IGF-1R blocker), erlotinib (anti-EGFR), and gemcitabine was compared with gemcitabine and erlotinib in the phase Ib/II study of patients with untreated metastatic pancreatic cancer. Unfortunately, the three-drug combination did not offer any benefit over gemcitabine/erlotinib [38].

The role of anti-Her2 treatment with trastuzumab in addition to chemotherapy in patients with metastatic pancreatic adenocarcinoma was investigated in small clinical trials. The addition of anti-Her2 treatment to chemotherapy did not add any meaningful benefit compared to chemotherapy alone, even in patients with Her2 amplification [39, 40]. The addition of the tyrosine kinase Her2 inhibitor lapatinib to gemcitabine also did not add any benefit compared to gemcitabine alone, and the trial was stopped early for futility [41].

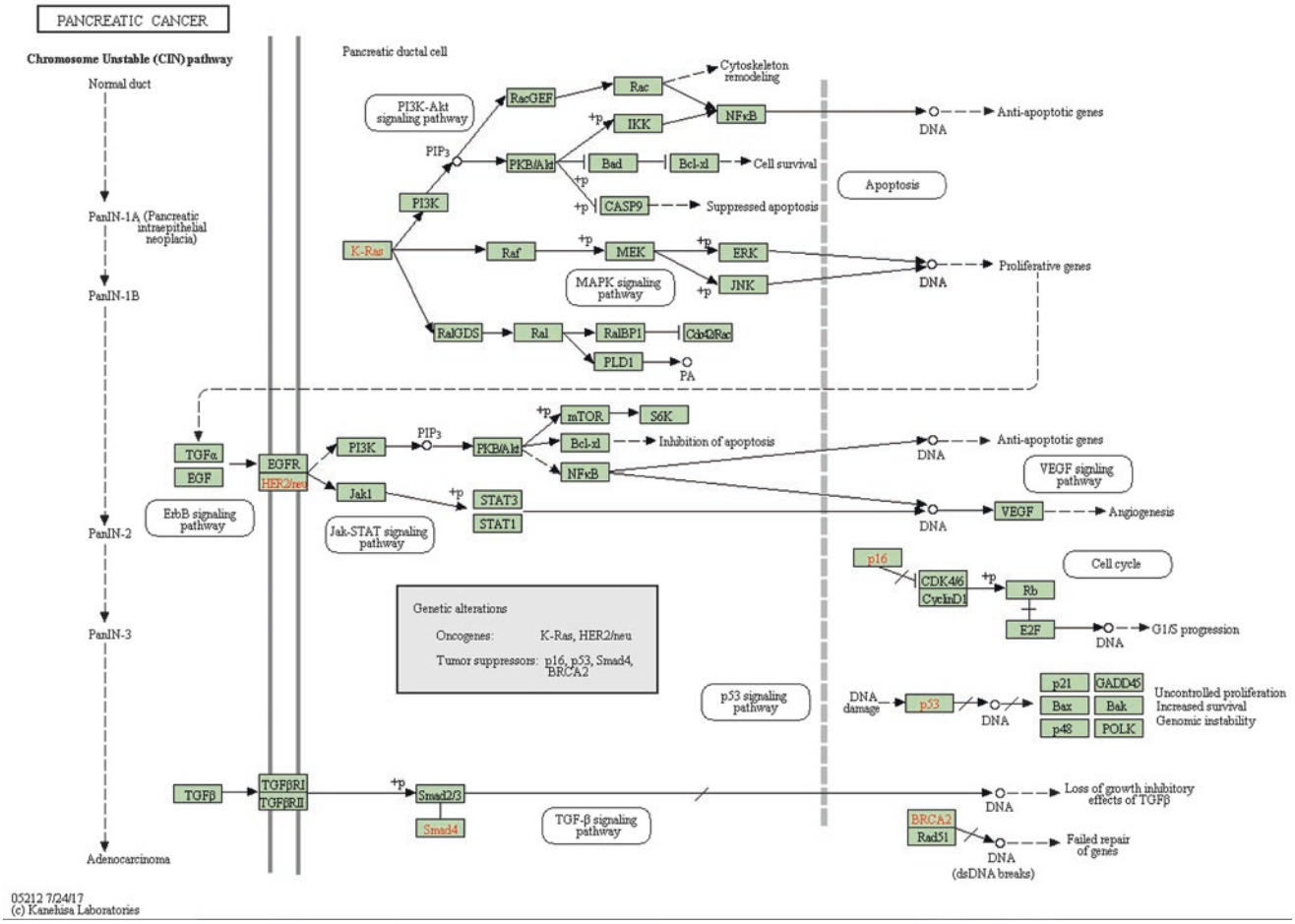


Fig. 15.1 Molecular alteration in oncogenesis of pancreatic ductal adenocarcinoma. The overexpression of HER-2/neu and activating point mutations in the *K-ras* gene occurs early, inactivation of the p16 gene at an intermediate stage, and the inactivation of *p53*, *SMAD4*, and *BRCA2* occurs relatively late [31, 32]. (Diagram reprinted with permission from KEGG Database: Pancreatic cancer—*Homo sapiens* (human). http://www.genome.jp/kegg-bin/show_pathway?hsa05212)

The combination of MEK inhibitor trametinib and pan class PI3K inhibitor buparlisib did not show any significant activity in metastatic pancreatic adenocarcinoma in a phase Ib dose-escalation study [42]. The combination of MEK inhibitor trametinib and everolimus (mTOR inhibitor) was tested in solid tumors including metastatic pancreatic adenocarcinoma in a phase Ib study. The study showed that combination was too toxic and that maximum tolerated dose could not be established. The combination did not show significant activity in the pancreatic patient population [43].

VEGF/VEGFR

Treatments targeting vascular endothelial growth factor (VEGF) and its receptors (VEGFR) were also studied in patients with metastatic pancreatic adenocarcinoma. A phase II study of sorafenib (multitageted tyrosine kinase inhibitor including VEGFR1, VEGFR2, VEGFR3, PDGFR, cKIT, FLT-3, the RAF/MEK/ERK pathways) with gemcitabine and erlotinib in the first-line setting for advanced pancreatic cancer did not show meaningful improvement in outcome [44]. A phase III study conducted by the Cancer and Leukemia Group B (CALGB 80303) showed that the addition of bevacizumab (10 mg/kg on days 1 and 15) to gemcitabine in patients with advanced disease did not improve survival outcomes compared to gemcitabine plus placebo [45]. A randomized phase III study investigated the addition of aflibercept to gemcitabine in patients with advanced pancreatic cancer who received no prior therapy, but the study was stopped for futility following a planned interim analysis as the experimental arm fared worse, though not statistically significant [46].

Hypoxia-Activated Agents

Tumoral hypoxia is considered an important mechanism for drug resistance and disease progression in pancreatic cancer. TH-302 (evofosfamide), a novel agent, is a hypoxia-activated

prodrug that in hypoxic settings releases the DNA alkylating agent bromo-isophosphoramide mustard. Even though the open-label phase II study of untreated advanced pancreatic cancer randomized 1:1:1 to receive gemcitabine alone (1000 mg/m^2 over 30 minutes), gemcitabine plus TH-302 at 240 mg/m^2, or gemcitabine plus TH-302 at 340 mg/m^2 showed improvement in overall survival in favor of the experimental arm [47], the phase III MAESTRO study that randomized patients between gemcitabine with placebo and gemcitabine with TH-302 did not show any difference in the survival outcomes of patients treated with experimental and control arms [48].

Targeting the Microenvironment

The pancreatic adenocarcinoma tumor microenvironment has been characterized by a dense stromal reaction with hypovascularity that contains overactive fibroblasts and immune-suppressive cells. Multiple attempts have been made to target different aspects of the tumor microenvironment.

Hedgehog Signaling

Hedgehog signaling has been recognized to be an essential pathway during embryonic development and in adult stem cells [49]. Paracrine hedgehog signaling from neoplastic cells to stromal myofibroblastic cells promotes stromal desmoplasia [50, 51]. Although it has been considered to have a role in pancreatic tumorigenesis and its depletion in the stroma was shown to increase delivery of chemotherapy in mouse models [52], clinical trials have shown hedgehog inhibitors (vismodegib and saridegib) to have no effect on tumor regression and patient survival [53, 54]. Some have argued that the stromal myofibroblasts may even have a protective role in supporting the local immune system, and inhibiting them may contribute to adverse outcomes from the cancer [53].

Hyaluronan

Hyaluronan is a non-sulfated glycosaminoglycan that is abundant in the extracellular matrix of human and murine pancreas adenocarcinoma. The tumor microenvironment of pancreatic adenocarcinoma is characterized by hypovascularity and extensive deposits of extracellular matrix components. Hyaluronan is a major component of the extracellular matrix and appears to be a barrier to diffusion of small-molecule therapy [55]. The enzymatic degradation of hyaluronan with PEGPH20 was shown to induce re-expansion of vasculature and improved delivery of chemotherapeutic drugs into the matrix of pancreatic adenocarcinoma in preclinical models [55, 56]. A recently completed phase II study investigated whether the addition of PEGPH20 to standard gemcitabine and nab-paclitaxel improved outcomes in untreated metastatic pancreatic adenocarcinoma. Though the final study outcomes are yet to be published, interim analysis of 146 patients showed improved median PFS in patients with HA-high tumors treated with PEGPH20 (9.2 vs 4.3 months; $P = 0.05$) [57]. A double-blind, randomized phase 3 study is currently ongoing in patients with metastatic pancreatic cancer with high expression of tumoral HA by immunohistochemistry [58].

JAK/STAT

The Janus kinase (*JAK*) and Signal transducer and activator (*STAT*) pathway transmits extracellular signals to the nucleus resulting in expression of genes involved in proliferation, apoptosis, oncogenesis, and immune regulation [59]. A phase II study compared capecitabine plus ruxolitinib (*JAK* inhibitor) versus capecitabine plus placebo in patients with metastatic pancreatic adenocarcinoma who have failed first-line therapy with gemcitabine. A modest improvement in OS was seen in the subgroup of patients with high C-reactive protein [60]. However, the phase III JANUS 1 clinical trial evaluating capecitabine plus ruxolitinib versus capecitabine plus placebo as second-line therapy in patients with advanced disease and evidence of a systemic inflammatory response was reported to be negative [61].

Targeting DNA Repair

It is estimated that less than 5% of pancreatic ductal adenocarcinomas are characterized by defective *BRCA2*, and an additional small percentage are characterized by defects in the related *PALB2*, part of Fanconi anemia genes. These genes play a crucial role in the repair of damaged DNA [62, 63]. Mutations in the DNA repair pathway genes (*BRCA2* and *PALB2*) are thought to confer sensitivity to platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors [64]. A next-generation sequencing study performed on multiple pancreatic ductal adenocarcinoma genomes estimated that a significant proportion of patients have defects in the DNA repair pathway that may predict susceptibility to platinum and/or PARP inhibition [65]. PARP inhibitors have shown clinical benefit in small subgroups of patients with defective DNA repair pathway including BRCA1 and 2 gene mutations [66, 67]. Multiple studies are ongoing to further evaluate the role of PARP inhibitors in patients with metastatic pancreatic carcinoma (with or without defective DNA repair pathways).

Targeting Macrophage

Macrophages that infiltrate the tumor microenvironment are responsible for disease progression and immune suppres-

sion that is characteristic of pancreatic cancers. CD40, a tumor necrosis factor receptor superfamily member, regulates activation of T cells and regulates cancer-associated inflammation and fibrosis. CD40 activation has been shown in preclinical studies to induce antitumor T-cell responses [68, 69]. CD40 agonists activate antigen-presenting cells, promoting an antitumor immune response. Monocytes infiltrate the tumor and degrade the stromal microenvironment, resulting in regression of the tumor [70]. A phase I study evaluated the fully human agonist CD40 monoclonal antibody CP-870,893 with full-dose gemcitabine in 22 patients with untreated advanced pancreatic cancer, demonstrating an ORR of 19% and stable disease in 50% of patients [71]. The CCL2-CCR2 chemokine axis has been implicated in the recruitment of tumor-associated macrophages for construction of an immunosuppressive tumor microenvironment [72]. The oral CCR2 inhibitor PF-04136309 was studied in combination with FOLFIRINOX (n = 39) and compared with FOLFIRINOX (n = 8) in a phase I, open-label clinical trial for treatment of locally advanced pancreatic cancer. The combination was well tolerated and showed an objective response rate of 49%, with local tumor control rate of 97%, unlike patients who only received FOLFIRINOX, who had no objective response rates, but had stable disease in 80%. In addition, patients who received the CCR2 inhibitor had reduced monocyte shift from the marrow to the peripheral blood. There was also a reduction in macrophages and regulatory T cells infiltrating the pancreatic tumor along with an increase in tumor-infiltrating CD4 and CD8 lymphocytes [73].

Studies evaluating novel CD40 agonists in combination with checkpoint inhibitors are ongoing.

Targeting Stem Cells

The stem cell factor inhibitor BBI608 blocks *STAT3*, which is critical for maintaining cancer stem cells, while it spares hematopoietic stem cells in mouse xenograft models of pancreatic cancer [74]. A phase I trial of necuparanib combined with gemcitabine and nab-paclitaxel demonstrated a 14.2-month OS and a disease control rate of 88% [75]. A phase Ib trial of BBI608 with gemcitabine and nab-paclitaxel in untreated metastatic pancreatic adenocarcinoma (adjuvant therapy allowed) is currently ongoing (NCT02231723). A phase III, open-label study of napabucasin plus nab-paclitaxel with gemcitabine in adult patients with metastatic pancreatic adenocarcinoma (CanStem111P) is also recruiting patients (NCT 02993731). In addition, the novel agent necuparanib targets pathways critical for the tumor microenvironment, including P-selectin, CXCR4/stromal cell-derived factor 1, vascular endothelial growth factor/fibroblast growth factor 2, and heparanase [75].

The notch pathway plays a central role in embryonic development and the regulation of stem and progenitor cells implicated in many human cancers. Pancreatic adenocarcinoma expressing Notch 3 has poor survival prognosis [76]. Tarextumab is a fully human IgG2 that inhibits both Notch 2 and Notch3 receptors. The addition of tarextumab to nab-paclitaxel and gemcitabine in a phase II study did not improve OS in patients with untreated metastatic pancreas adenocarcinoma, and study was stopped prematurely [75].

Immunotherapy

Challenges in Immunotherapy

Response to immune therapy is generally seen in cancers that have inflamed tumor phenotype, such as melanoma [77]. On the other hand, pancreatic cancer has non-inflamed phenotype and contains an immunosuppressive microenvironment roughly containing immune and inflammatory cells with an abundance of inhibitory regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC), and macrophages with scarcity of effector cytotoxic T cells [78, 79]. Many trials that tested different forms of immunotherapy in pancreatic cancer have been unsuccessful to show a clinical benefit. This presents a major challenge for the development of new treatment paradigms as we are now seeing that pancreatic cancer is not responsive to immunotherapy in addition to being chemoresistant.

Vaccines

Cancer vaccines are designed to activate the adaptive immune response to cancer by stimulating dendritic cells to specific tumor antigen presentation. These vaccinations are based on overexpressed antigens in pancreatic ductal adenocarcinoma cells. Several types of cancer vaccines have been tested in pancreatic cancer, such as whole-cell vaccines, peptides, *Listeria* species, dendritic cells, etc. [80]. So far, despite a seemingly rational scientific concept underlying the design of the vaccines, no vaccine has proven clinical efficacy.

Whole-Cell Vaccines

The GVAX pancreas vaccine is an allogeneic whole-cell vaccine transfected with granulocyte-macrophage colony-stimulating factor, which acts as a maturation factor for the antigen-presenting cells/dendritic cells [80]. GVAX vaccine was studied with adjuvant chemoradiotherapy after resection of pancreatic cancer in a phase II study, and showed modest median disease-free and overall survival rates of 17.3 and 24.8 months, respectively [81]. For patients with metastatic pancreatic cancer, a randomized phase II study tested the

GVAX vaccine combined with a boost of live-attenuated *Listeria monocytogenes* vaccine modified to deliver the pancreatic tumor antigen mesothelin (CRS-207) versus GVAX alone. The GVAX vaccine was administered after low-dose cyclophosphamide to inhibit regulatory T cells. Among 90 patients, 51% previously treated with ≥2 lines of chemotherapy, the median OS was 6.1 versus 3.9 months for the GVAX + CRS-207 vaccine therapy versus GVAX alone, and toxicity was manageable [82]. A larger phase IIb randomized multicenter 3-arm trial of GVAX plus CRS-207 versus CRS-207 alone versus chemotherapy was conducted in patients with refractory metastatic pancreatic adenocarcinoma (ECLIPSE, NCT02004262), but neither of the vaccine arms showed better outcomes compared to the chemotherapy arm [83]. The administration of GVAX pancreas vaccine prior to surgical resection has shown evidence of tumor infiltration by immune mediators. Whether this will have therapeutic impact in the outcomes of the patients remains to be seen [84]. The combination of GVAX pancreas vaccine with the anti-CTLA-4 ipilimumab was tested in a randomized study versus ipilimumab alone, for patients with previously treated locally advanced or metastatic pancreatic cancer. The median overall survival rates were 5.7 months with the combination and 3.6 months with ipilimumab alone [85]. Studies are currently being conducted evaluating the combination of the GVAX vaccine and immune checkpoint inhibitor and chemotherapy in patients with pancreatic cancer.

Algenpantucel-L is an irradiated human allogeneic pancreatic cancer cell line genetically engineered to express the murine enzyme α(alpha)-1, 3-galactosyl transferase (α[alpha] GT). As humans naturally do not express α(alpha)Gal epitopes but possess large amounts of anti-α(alpha)Gal antibodies, the vaccination with algenpantucel-L may result in destruction of the vaccine cells via the complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity (ADCC). The release of cancer cell antigens from the vaccine cells may result in the activation of the immune system, as observed in transplant rejection [86]. Even though earlier phase studies of the vaccine showed promising results, the phase III adjuvant study of algenpantucel-L and chemoradiotherapy for patients with resected pancreatic cancer (NCT01072981) was unfortunately negative [87].

Peptide Vaccine

Peptide vaccines are based on cancer-specific peptides capable of binding human leukocyte antigen class molecules and activating a CD4/CD8 immune response. Vaccine trials that used peptides so far have been negative. Mutant *KRAS* peptide vaccines with granulocyte macrophage colony-stimulating factor (GMCSF) have been evaluated after surgical resection of pancreatic cancer. Although the vaccine was well tolerated, there was no detectable immunogenicity and unproven efficacy [88]. Telomerase is a ribonucleotide enzyme that maintains telomeres and confers cancer cells immortality. The telomerase peptide vaccine GV1001 did not improve survival when combined sequentially or concurrently with gemcitabine/capecitabine chemotherapy compared to chemotherapy alone in the Phase III randomized TeloVac trial [89].

Vector-Based Vaccines

Viral vectors are engineered to carry genes coding a target antigen; therefore the transfected gene will be immunogenic. Viral vector expressing CEA, MUC-1, and TRICOM® (TRIad of COstimulatory Molecules; a vaccine containing 3 costimulatory molecules: B7.1, ICAM-1, and LFA-3) was named PANVAC. Although the PANVAC vaccine was well tolerated and had some promising findings in earlier phase studies, a phase III clinical trial of single-agent PANVAC in patients with pancreatic cancer was a negative trial and did not improve survival compared to placebo alone [90].

Immune Checkpoint Inhibitors

Immune checkpoints are built-in inhibitory mechanisms that prevent the perpetual activation of the immune system. Overexpression of ligands of these immune checkpoints by cancer cells effectively dampens the immune response against the malignant cell [91]. Tumor cell expression of PD-L1 in pancreatic cancer has been associated with reduced survival and an unfavorable prognosis [92–94].

Immune checkpoint inhibitors, such as agents that block the anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and anti-programmed death 1 (anti-PD-1), are currently approved by the FDA for the treatment of melanoma and non-small-cell lung cancer. These agents and others immune checkpoint inhibitors have been the focus of cancer research in many cancers in the last few years, effectively opening a new frontier in cancer treatment in general.

Programmed death ligand 1 (PD-L1) on the tumor cell's surface modulates the immune system by dampening the local T-cell response and cytokine production during inflammation to avoid detection [91]. Tumor cell expression of PD-L1 is upregulated in a broad range of cancers with a high frequency including pancreatic carcinomas [92–94], and this has been associated with reduced survival and an unfavorable prognosis.

A phase II study evaluating the use of ipilimumab (anti-CTLA-4 antibody) as a single-agent treatment for pancreatic cancer was disappointing, although one patient had shown a durable treatment response [95]. The combination of the whole-cell vaccine GVAX with ipilimumab when compared to single-agent ipilimumab in a phase Ib trial of 30 patients with pretreated advanced disease did not show statistically significant difference [85]. The phase 2b, randomized, multicenter study of GVAX pancreas and CRS-207 compared to

chemotherapy in adults with previously treated metastatic pancreatic adenocarcinoma (ECLIPSE Study) was recently reported negative [96].

A larger phase II trial of GVAX with cyclophosphamide and CRS-207, with or without nivolumab as second-line treatment in metastatic pancreatic adenocarcinoma (STELLAR), is currently ongoing, and results are being awaited [97]. There was no response seen from treatment with anti-PD-L1 in pancreatic cancer patients [98].

Biomarkers

One of the challenges of treating patients with pancreatic carcinoma is the unavailability of a reliable biomarker that helps predict response or resistance to a given standard of care treatment. Newer treatments currently being studied have some biomarkers that are being used to select patients. Blood level of CA19-9 has traditionally been used to follow the activity of pancreatic adenocarcinoma, but it lacks specificity as it is also elevated in other upper gastrointestinal tumors and benign pancreatobiliary conditions [99]. Additionally, not all pancreatic carcinomas reliably have elevated levels of CA19-9. The level of CA19-9 does not predict response or resistance to treatment [100]. This has persuaded scientists to search for a better and more predictive biomarker, which is yet to be discovered.

hENT1

Human equilibrative nucleoside transporter 1 (hENT1) provides the major route for gemcitabine to enter a cell, and it is one of the most extensively studied biomarkers in the context of gemcitabine response [101]. The overexpression of hENT1 in the tumor has been linked to response to gemcitabine therapy [102]. However, the limited therapeutic benefit of gemcitabine in general makes this marker less appealing.

SPARC

Secreted protein acidic and rich in cysteine (SPARC) is a matricellular glycoprotein that has been implicated in tumor stroma interactions in pancreatic cancer. It is expressed in high proportion in pancreatic adenocarcinoma in comparison with normal pancreatic tissue [103]. Although its exact role in the pathogenesis has not been well established, its overexpression has been associated with poorer prognosis. Moreover, nano albumin-bound paclitaxel has been seen to sequester in proximity to the tumor when there is high expression of SPARC as it has high affinity for albumin. As SPARC deficiency in tumors did not affect intratumoral paclitaxel concentration, its exact effect on nab-paclitaxel is not clear. SPARC has been shown to have both oncogenic and tumor suppressor properties. There is no clear association between the levels of SPARC in the serum, pancreatic juice, or ascites with patient outcome or treatment response [104].

Hyaluronan

Hyaluronan is a non-sulfated glycosaminoglycan that is abundant in the extracellular matrix of human and murine pancreas adenocarcinoma that contributes to the barrier to perfusion of small-molecule chemotherapy [55]. Patients with tumors that have high levels of hyaluronan have particularly responded better to treatment with combination of PEGPH20 and chemotherapy compared to patients with low levels of hyaluronan in their tumors [57]. If the double-blind, randomized phase 3 study becomes positive [58], this biomarker may be useful in the selection of patients for treatment with this regimen.

BRCA1/2

Given the infrequent nature of BRCA gene mutation in patients with pancreas cancer (less than 5% of pancreatic ductal adenocarcinomas), the clinical utility of this gene mutation as a biomarker is limited. These genes play a crucial role in the repair of damaged DNA [62, 63]. The presence of this gene mutation may confer treatment benefit from chemotherapy drugs that damage DNA (e.g., platinum drugs) or inhibitors of the poly (ADP-ribose) polymerase (PARP), which has been very well described in pancreatic and other cancers [64, 65]. PARP inhibitors have shown clinical benefit in small subgroups of patients with defective DNA repair pathways including BRCA1 and 2 gene mutations [66, 67]. The presence of BRCA gene mutation may be considered a predictive marker for response with such treatments like PARP inhibitors, if they ever become approved for use.

UGT1A1

Polymorphism in the uridine diphosphate glucuronosyltransferase (UGT) 1A1 gene has been linked to increased hematologic toxicity to irinotecan-containing chemotherapy [105, 106]. It has been proposed to use the presence of UGT1A1 polymorphism to identify the patients that are likely to experience severe neutropenia while considering irinotecan-based regimens such as FOLFIRINOX or FOLFIRI. The gene polymorphism does not have other roles like indirect reflection of tumor burden.

Challenges of Systemic Therapies

The main challenge in treating patients with pancreatic carcinoma is that the disease is resistant to chemotherapy and other modern treatment approaches. In addition to being resistant to treatments, the disease follows an aggressive course leading to systemic symptoms such as anorexia, cachexia, venous thromboembolism, rapid functional decline, and metastases-related symptoms such as ascites or liver failure. It is not uncommon to see patients decline rapidly beyond the frontline regimen to the extent they will not be able to tolerate further treatments. Most patients diagnosed with the cancer die within the first year of diagnosis. Some of this may be merely due to the lack of effective and well-tolerated treatment options. Although it sounds counterintuitive, most of the systemic symptoms of the disease are ameliorated using chemotherapy and patients feel better for a brief period despite being on aggressive chemotherapy regimen. As most novel treatment approaches have failed to work in pancreatic cancer, it is less likely that we will find the silver bullet that treats this aggressive cancer. The treatment that may be able to control the disease is likely a combination of different novel approaches.

The other problem is that many patients diagnosed with this disease are older than 65 years. As many of the trials actually included older patients, we do not see age alone playing a decisive role in the selection of treatments. As pancreas cancer is a systemic disease from the outset in many of the patients, a multidisciplinary approach to managing the patient's symptoms is imperative. These patients often require nutritional support, treatment for pancreatic insufficiency and the resulting malabsorption, palliative decompressive procedures directed at the biliary system, and aggressive pain management.

Conclusion

In the last few decades, a modest improvement in treatment response has been shown to result from the use of a more complex and intensive chemotherapy regimen in patients with pancreatic carcinoma. Many novel treatment approaches targeting altered intracellular pathways, the immune system, and the tumor stroma have been disappointingly negative. There are still some ongoing studies for which we are expecting good outcomes with a degree of optimism (Table 15.2).

Table 15.2 List of selected ongoing trials in pancreatic carcinoma

Clinical trials	Study title	Disease stage	Phase
Cytotoxic chemotherapy			
NCT02352337	Randomized Phase II Study in Metastatic Pancreatic Cancer Evaluating FOLFIRINOX +/− LV5FU2 in Maintenance Versus FIRGEM in First-line	IV	II
NCT02620800	Study of 5-fluorouracil (5-FU), Nab-paclitaxel, Bevacizumab, Leucovorin, and Oxaliplatin in Patients With Metastatic Pancreatic Cancer (FABLOx)	IV	II
NCT02551991	A Randomized, Open-label Phase 2 Study of Nanoliposomal Irinotecan (Nal-IRI)-Containing Regimens Versus Nab-Paclitaxel Plus Gemcitabine in Patients With Previously Untreated, Metastatic Pancreatic Adenocarcinoma	IV	II
NCT02890355	Randomized Phase II Study of 2nd Line FOLFIRI Versus Modified FOLFIRI With PARP Inhibitor ABT-888 (Veliparib) (NSC-737664) in Metastatic Pancreatic Cancer	IV	II
BRCA			
NCT02184195	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients With gBRCA Mutated Metastatic Pancreatic Cancer Whose Disease Has Not Progressed on First-line Platinum Based Chemotherapy	IV	III
CXCL12/CXCR4 axis			
NCT02826486	A Phase II, Multicenter, Open-label Single Arm Study to Assess the Safety and Efficacy of the Combination of BL-8040 and Pembrolizumab in Patients With Metastatic Pancreatic Cancer, the COMBAT Study	IV	II
CSF1/CSF1R axis			
NCT02777710	A Dose Escalation Phase I Study With an Extension Part Evaluating the Safety and Activity of an Anti-PDL1 Antibody (DURVALUMAB) Combined With a Small Molecule CSF-1R Tyrosine Kinase Inhibitor (PEXIDARTINIB) in Patients With Metastatic/Advanced Pancreatic or Colorectal Cancers	III/IV	I
CCL2/CCR2 axis			
NCT02732938	Ph1b/2 Study of Pf-04136309 in Combination With Gem/Nab-P in First-line Metastatic Pancreatic Patients (CCR2i)	IV	Ib/ II
Stroma—PEGPH20			
NCT01959139	A Phase Ib/II Randomized Study Of Modified Folfirinox + Pegylated Recombinant Human Hyaluronidase (PEGPH20) Versus Modified FOLFIRINOX Alone In Patients With Good Performance Status Metastatic Pancreatic Adenocarcinoma	IV	Ib/ II
NCT02715804	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination With Nab-Paclitaxel Plus Gemcitabine Compared With Placebo Plus Nab-Paclitaxel and Gemcitabine in Participants With Hyaluronan-High Stage IV Previously Untreated Pancreatic Ductal Adenocarcinoma	IV	III

Nevertheless, the treatment benefits observed from newer treatments of pancreatic cancer have only been incrementally modest. A multipronged approach is probably needed to see a more robust result. From all the negative studies, it is clear that a single-treatment approach will not work. We recommend increasing collaboration among scientists and to accelerate discovery of new treatment approaches.

References

1. Chiorean EG, Coveler AL. Pancreatic cancer: optimizing treatment options, new, and emerging targeted therapies. Drug Des Devel Ther. 2015;9:3529–45.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7–30.
3. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol. 2012;23(4):843–52.
4. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer (Oxford, England: 1990). 2011;47(13):1928–37.
5. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the international pancreatic cancer case-control consortium (panc4). Ann Oncol. 2012;23(7):1880–8.
6. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the international pancreatic cancer case-control consortium (panc4). Ann Oncol. 2012;23(11):2964–70.
7. Jones S, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, et al. Exomic sequencing identifies palb2 as a pancreatic cancer susceptibility gene. Science (New York, NY). 2009;324(5924):217.
8. Iqbal J, Ragone A, Lubinski J, Lynch HT, Moller P, Ghadirian P, et al. The incidence of pancreatic cancer in brca1 and brca2 mutation carriers. Br J Cancer. 2012;107(12):2005–9.
9. Rebours V, Boutron-Ruault MC, Schnee M, Ferec C, Maire F, Hammel P, et al. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series. Am J Gastroenterol. 2008;103(1):111–9.
10. Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, et al. Risk of pancreatic cancer in families with lynch syndrome. JAMA. 2009;302(16):1790–5.
11. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial peutz-jeghers syndrome. Gastroenterology. 2000;119(6):1447–53.
12. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
13. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
14. Chiorean EG, Von Hoff DD, Tabernero J, El-Maraghi R, Ma WW, Reni M, et al. Second-line therapy after nab-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. Br J Cancer. 2016;115(2):188–94.
15. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403–13.
16. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the national cancer institute of canada clinical trials group. J Clin Oncol. 2007;25(15):1960–6.
17. Wang-Gillam A, Li C-P, Bodoky G, Dean A, Shan Y-S, Jameson GS, et al. Updated overall survival analysis of napoli-1: Phase III study of nanoliposomal irinotecan (nal-IRI, MM-398), with or without 5-fluorouracil and leucovorin (5-FU/LV), versus 5-FU/LV in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy. ASCO Meet Abstr. 2016;34(4_suppl):417.
18. Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the conko-003 trial. J Clin Oncol. 2014;32(23):2423–9.
19. Xiong HQ, Varadhachary GR, Blais JC, Hess KR, Abbruzzese JL, Wolff RA. Phase 2 trial of oxaliplatin plus capecitabine (xelox) as second-line therapy for patients with advanced pancreatic cancer. Cancer. 2008;113(8):2046–52.
20. Yoo C, Hwang JY, Kim JE, Kim TW, Lee JS, Park DH, et al. A randomised phase II study of modified folfiri.3 vs modified folfox as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. Br J Cancer. 2009;101(10):1658–63.
21. Ghosn M, Farhat F, Kattan J, Younes F, Moukadem W, Nasr F, et al. Folfox-6 combination as the first-line treatment of locally advanced and/or metastatic pancreatic cancer. Am J Clin Oncol. 2007;30(1):15–20.
22. Boeck S, Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, et al. Capecitabine plus oxaliplatin (capox) versus capecitabine plus gemcitabine (capgem) versus gemcitabine plus oxaliplatin (mgemox): final results of a multicenter randomized phase ii trial in advanced pancreatic cancer. Ann Oncol. 2008;19(2):340–7.
23. Novarino A, Satolli MA, Chiappino I, Giacobino A, Bellone G, Rahimi F, et al. Oxaliplatin, 5-fluorouracil, and leucovorin as second-line treatment for advanced pancreatic cancer. Am J Clin Oncol. 2009;32(1):44–8.
24. Zaanan A, Trouilloud I, Markoutsaki T, Gauthier M, Dupont-Gossart AC, Lecomte T, et al. Folfox as second-line chemotherapy in patients with pretreated metastatic pancreatic cancer from the firgem study. BMC Cancer. 2014;14:441.
25. Chung JW, Jang HW, Chung MJ, Park JY, Park SW, Chung JB, et al. Folfox4 as a rescue chemotherapy for gemcitabine-refractory pancreatic cancer. Hepatogastroenterology. 2013;60(122):363–7.
26. Gill S, Ko Y-JJ, Cripps C, Beaudoin A, Dhesy-Thind S, Zulfiqar M, et al. Pancreox: a randomized phase III study of 5-fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. J Clin Oncol. 2016;34:3914–20.
27. Portal A, Pernot S, Tougeron D, Arbaud C, Bidault AT, de la Fouchardiere C, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after folfirinox failure: an ageo prospective multicentre cohort. Br J Cancer. 2015;113(7):989–95.
28. Gebbia V, Maiello E, Giuliani F, Borsellino N, Arcara C, Colucci G. Irinotecan plus bolus/infusional 5-fluorouracil and leucovorin in patients with pretreated advanced pancreatic carcinoma: a multicenter experience of the gruppo oncologico italia meridionale. Am J Clin Oncol. 2010;33(5):461–4.
29. Neuzillet C, Hentic O, Rousseau B, Rebours V, Bengrine-Lefevre L, Bonnetain F, et al. Folfiri regimen in metastatic pancreatic adenocarcinoma resistant to gemcitabine and platinum-salts. World J Gastroenterol. 2012;18(33):4533–41.

30. Yachida S, Iacobuzio-Donahue CA. Evolution and dynamics of pancreatic cancer progression. Oncogene. 2013;32(45):5253–60.
31. Kanehisa M, Sato Y, Kawashima M, Furumichi M, Tanabe M. Kegg as a reference resource for gene and protein annotation. Nucleic Acids Res. 2016;44(D1):D457–62.
32. Kanehisa M, Furumichi M, Tanabe M, Sato Y, Morishima K. Kegg: new perspectives on genomes, pathways, diseases and drugs. Nucleic Acids Res. 2017;45(D1):D353–61.
33. Hruban RH, Wilentz RE, Maitra A. Identification and analysis of precursors to invasive pancreatic cancer. Methods Mol Med. 2005;103:1–13.
34. di Magliano MP, Logsdon CD. Roles for kras in pancreatic tumor development and progression. Gastroenterology. 2013;144(6):1220–9.
35. Bryant KL, Mancias JD, Kimmelman AC, Der CJ. Kras: feeding pancreatic cancer proliferation. Trends Biochem Sci. 2014;39(2):91–100.
36. Chung V, McDonough S, Philip PA, Cardin D, Wang-Gillam A, Hui L, et al. Effect of selumetinib and MK-2206 vs oxaliplatin and fluorouracil in patients with metastatic pancreatic cancer after prior therapy: SWOG S1115 study randomized clinical trial. JAMA Oncol. 2017;3:516–22.
37. Philip PA, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: southwest oncology group-directed intergroup trial s0205. J Clin Oncol. 2010;28(22):3605–10.
38. Philip PA, Goldman B, Ramanathan RK, Lenz HJ, Lowy AM, Whitehead RP, et al. Dual blockade of epidermal growth factor receptor and insulin-like growth factor receptor-1 signaling in metastatic pancreatic cancer: phase Ib and randomized phase II trial of gemcitabine, erlotinib, and cixutumumab versus gemcitabine plus erlotinib (swog s0727). Cancer. 2014;120(19):2980–5.
39. Safran H, Iannitti D, Ramanathan R, Schwartz JD, Steinhoff M, Nauman C, et al. Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress her-2/neu. Cancer Invest. 2004;22(5):706–12.
40. Harder J, Ihorst G, Heinemann V, Hofheinz R, Moehler M, Buechler P, et al. Multicentre phase II trial of trastuzumab and capecitabine in patients with Her2 overexpressing metastatic pancreatic cancer. Br J Cancer. 2012;106(6):1033–8.
41. Safran H, Miner T, Bahary N, Whiting S, Lopez CD, Sun W, et al. Lapatinib and gemcitabine for metastatic pancreatic cancer. a phase II study. Am J Clin Oncol. 2011;34(1):50–2.
42. Bedard PL, Tabernero J, Janku F, Wainberg ZA, Paz-Ares L, Vansteenkiste J, et al. A phase Ib dose-escalation study of the oral pan-PI3K inhibitor buparlisib (BKM120) in combination with the oral mek1/2 inhibitor trametinib (GSK1120212) in patients with selected advanced solid tumors. Clin Cancer Res. 2015;21(4):730–8.
43. Tolcher AW, Bendell JC, Papadopoulos KP, Burris HA 3rd, Patnaik A, Jones SF, et al. A phase IB trial of the oral mek inhibitor trametinib (GSK1120212) in combination with everolimus in patients with advanced solid tumors. Ann Oncol. 2015;26(1):58–64.
44. Cohen DJ, Leichman LP, Love E, Ryan T, Leichman CG, Newman E, et al. Phase II study of sorafenib with gemcitabine and erlotinib (ges) in first-line advanced pancreatic cancer. J Clin Oncol (Meeting Abstracts). 2011;29(Suppl 4):abstract 266.
45. Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: Phase III trial of the cancer and leukemia group B (CALGB 80303). J Clin Oncol. 2010;28(22):3617–22.
46. Rougier P, Riess H, Manges R, Karasek P, Humblet Y, Barone C, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. Eur J Cancer (Oxford, England: 1990). 2013;49(12):2633–42.
47. Borad MJ, Reddy SG, Bahary N, Uronis HE, Sigal D, Cohn AL, et al. Randomized phase II trial of gemcitabine plus TH-302 versus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2015;33(13):1475–81.
48. Cutsem EV, Lenz H-J, Furuse J, Tabernero J, Heinemann V, Ioka T, et al. Evofosfamide (TH-302) in combination with gemcitabine in previously untreated patients with metastatic or locally advanced unresectable pancreatic ductal adenocarcinoma: primary analysis of the randomized, double-blind phase III maestro study. J Clin Oncol (Meeting Abstracts). 2016;34(Suppl 4S):abstract 193.
49. Thayer SP, di Magliano MP, Heiser PW, Nielsen CM, Roberts DJ, Lauwers GY, et al. Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis. Nature. 2003;425(6960):851–6.
50. Bailey JM, Swanson BJ, Hamada T, Eggers JP, Singh PK, Caffery T, et al. Sonic hedgehog promotes desmoplasia in pancreatic cancer. Clin Cancer Res. 2008;14(19):5995–6004.
51. Yauch RL, Gould SE, Scales SJ, Tang T, Tian H, Ahn CP, et al. A paracrine requirement for hedgehog signalling in cancer. Nature. 2008;455(7211):406–10.
52. Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, et al. Inhibition of hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science (New York, NY). 2009;324(5933):1457–61.
53. Lou K-J. Stromal uncertainties in pancreatic cancer. Sci Bus eXch. 2014;7(23):1–3.
54. Kim EJ, Sahai V, Abel EV, Griffith KA, Greenson JK, Takebe N, et al. Pilot clinical trial of hedgehog pathway inhibitor GDC-0449 (vismodegib) in combination with gemcitabine in patients with metastatic pancreatic adenocarcinoma. Clin Cancer Res. 2014;20(23):5937–45.
55. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21(3):418–29.
56. Jacobetz MA, Chan DS, Neesse A, Bapiro TE, Cook N, Frese KK, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut. 2013;62(1):112–20.
57. Hingorani SR, Harris WP, Hendifar AE, Bullock AJ, Wu XW, Huang Y, et al. High response rate and PFS with PEGPH20 added to nab-paclitaxel/gemcitabine in stage IV previously untreated pancreatic cancer patients with high-ha tumors: interim results of a randomized phase II study. J Clin Oncol (Meeting Abstracts). 2015;33(Suppl):abstract 4006.
58. Therapeutics H. A study of pegylated recombinant human hyaluronidase in combination with nab-paclitaxel plus gemcitabine compared with placebo plus nab-paclitaxel and gemcitabine in participants with hyaluronan-high stage iv previously untreated pancreatic ductal adenocarcinoma. Nct02715804. 2016, March 16 [cited 2017 January 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT02715804?term=pegph20&rank=13.
59. Aaronson DS, Horvath CM. A road map for those who don't know jak-stat. Science (New York, NY). 2002;296(5573):1653–5.
60. Hurwitz HI, Uppal N, Wagner SA, Bendell JC, Beck JT, Wade SM 3rd, et al. Randomized, double-blind, phase II study of ruxolitinib or placebo in combination with capecitabine in patients with metastatic pancreatic cancer for whom therapy with gemcitabine has failed. J Clin Oncol. 2015;33(34):4039–47.
61. Hurwitz H, Cutsem EV, Bendell JC, Hidalgo M, Li C-P, Garrido M, et al. Two randomized, placebo-controlled phase 3 studies of ruxolitinib (Rux) + capecitabine (C) in patients (pts) with advanced/metastatic pancreatic cancer (mPC) after failure/intolerance of first-line chemotherapy: Janus 1 (J1) and janus 2 (J2). J Clin Oncol (Meeting Abstracts). 2017;35(Suppl 4S):abstract 343.

62. Goggins M, Offerhaus GJ, Hilgers W, Griffin CA, Shekher M, Tang D, et al. Pancreatic adenocarcinomas with DNA replication errors (RER+) are associated with wild-type K-ras and characteristic histopathology. Poor differentiation, a syncytial growth pattern, and pushing borders suggest rer+. Am J Pathol. 1998;152(6):1501–7.
63. Zhen DB, Rabe KG, Gallinger S, Syngal S, Schwartz AG, Goggins MG, et al. BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: a pacgene study. Genet Med. 2015;17(7):569–77.
64. Lowery MA, Kelsen DP, Stadler ZK, Yu KH, Janjigian YY, Ludwig E, et al. An emerging entity: pancreatic adenocarcinoma associated with a known brca mutation: clinical descriptors, treatment implications, and future directions. Oncologist. 2011;16(10):1397–402.
65. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
66. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline brca1/2 mutation. J Clin Oncol. 2015;33(3):244–50.
67. Pishvaian MJ, Wang H, Zhuang T, He AR, Hwang JJ, Hankin A, et al. A phase I/II study of ABT-888 in combination with 5-fluorouracil (5-FU) and oxaliplatin (Ox) in patients with metastatic pancreatic cancer (MPC). J Clin Oncol (Meeting Abstracts). 2013;31(Suppl 4):abstract 147.
68. Bennett SR, Carbone FR, Karamalis F, Flavell RA, Miller JF, Heath WR. Help for cytotoxic-T-cell responses is mediated by CD40 signalling. Nature. 1998;393(6684):478–80.
69. Schoenberger SP, Toes RE, van der Voort EI, Offringa R, Melief CJ. T-cell help for cytotoxic T lymphocytes is mediated by CD40-CD40L interactions. Nature. 1998;393(6684):480–3.
70. Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. Science (New York, NY). 2011;331(6024):1612–6.
71. Beatty GL, Torigian DA, Chiorean EG, Saboury B, Brothers A, Alavi A, et al. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. Clin Cancer Res. 2013;19(22):6286–95.
72. Sanford DE, Belt BA, Panni RZ, Mayer A, Deshpande AD, Carpenter D, et al. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. Clin Cancer Res. 2013;19(13):3404–15.
73. Nywening TM, Wang-Gillam A, Sanford DE, Belt BA, Panni RZ, Cusworth BM, et al. Targeting tumour-associated macrophages with CCR2 inhibition in combination with folfirinox in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. Lancet Oncol. 2016;17(5):651–62.
74. Li Y, Rogoff HA, Keates S, Gao Y, Murikipudi S, Mikule K, et al. Suppression of cancer relapse and metastasis by inhibiting cancer stemness. Proc Natl Acad Sci U S A. 2015;112(6):1839–44.
75. O'Reilly EM, Sahai V, Bendell JC, Bullock AJ, LoConte NK, Hatoum H, et al. Results of a randomized phase ii trial of an anti-notch 2/3, tarextumab (omp-59r5, trxt, anti-notch2/3), in combination with nab-paclitaxel and gemcitabine (nab-p+gem) in patients (pts) with untreated metastatic pancreatic cancer (mpc). J Clin Oncol (Meeting Abstracts). 2017;35(Suppl 4S):abstract 279.
76. Mann CD, Bastianpillai C, Neal CP, Masood MM, Jones DJ, Teichert F, et al. Notch3 and HEY-1 as prognostic biomarkers in pancreatic adenocarcinoma. PLoS One. 2012;7(12):e51119.
77. Gajewski TF, Fuertes M, Spaapen R, Zheng Y, Kline J. Molecular profiling to identify relevant immune resistance mechanisms in the tumor microenvironment. Curr Opin Immunol. 2011;23(2):286–92.
78. Clark CE, Hingorani SR, Mick R, Combs C, Tuveson DA, Vonderheide RH. Dynamics of the immune reaction to pancreatic cancer from inception to invasion. Cancer Res. 2007;67(19):9518–27.
79. Stromnes IM, Brockenbrough JS, Izeradjene K, Carlson MA, Cuevas C, Simmons RM, et al. Targeted depletion of an MDSC subset unmasks pancreatic ductal adenocarcinoma to adaptive immunity. Gut. 2014;63(11):1769–81.
80. Salman B, Zhou D, Jaffee EM, Edil BH, Zheng L. Vaccine therapy for pancreatic cancer. Oncoimmunology. 2013;2(12):e26662.
81. Lutz E, Yeo CJ, Lillemoe KD, Biedrzycki B, Kobrin B, Herman J, et al. A lethally irradiated allogeneic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine for pancreatic adenocarcinoma. A phase II trial of safety, efficacy, and immune activation. Ann Surg. 2011;253(2):328–35.
82. Le DT, Wang-Gillam A, Picozzi V, Greten TF, Crocenzi T, Springett G, et al. Safety and survival with GVAX pancreas prime and *listeria monocytogenes*-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. J Clin Oncol. 2015;33(12):1325–33.
83. Le DT, Ko AH, Wainberg ZA, Picozzi VJ, Kindler HL, Wang-Gillam A, et al. Results from a phase 2b, randomized, multicenter study of GVAX pancreas and CRS-207 compared to chemotherapy in adults with previously-treated metastatic pancreatic adenocarcinoma (eclipse study). J Clin Oncol (Meeting Abstracts). 2017;35(Suppl 4S):abstract 345.
84. Lutz ER, Wu AA, Bigelow E, Sharma R, Mo G, Soares K, et al. Immunotherapy converts nonimmunogenic pancreatic tumors into immunogenic foci of immune regulation. Cancer Immunol Res. 2014;2(7):616–31.
85. Le DT, Lutz E, Uram JN, Sugar EA, Onners B, Solt S, et al. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. J Immunother. 2013;36(7):382–9.
86. Rossi GR, Mautino MR, Unfer RC, Seregina TM, Vahanian N, Link CJ. Effective treatment of preexisting melanoma with whole cell vaccines expressing alpha(1,3)-galactosyl epitopes. Cancer Res. 2005;65(22):10555–61.
87. Broderick JM. Pancreatic cancer vaccine falls short in phase III trial. [Website]: Onclive; 2016 [updated May 10, 2016 February 9, 2017]. Available from: http://www.onclive.com/web-exclusives/pancreatic-cancer-vaccine-falls-short-in-phase-iii-trial#sthash.nF1Uu8Ly.dpuf.
88. Abou-Alfa GK, Chapman PB, Feilchenfeldt J, Brennan MF, Capanu M, Gansukh B, et al. Targeting mutated K-ras in pancreatic adenocarcinoma using an adjuvant vaccine. Am J Clin Oncol. 2011;34(3):321–5.
89. Middleton G, Silcocks P, Cox T, Valle J, Wadsley J, Propper D, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. Lancet Oncol. 2014;15(8):829–40.
90. PRNewswire. Therion reports results of phase 3 panvac-vf trial. [Website]: PR Newswire; 2006 [December 1, 2015]. Available from: http://www.prnewswire.com/news-releases/therion-reports-results-of-phase-3-panvac-vf-trial-and-announces-plans-for-company-sale-56997582.html.
91. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002;8(8):793–800.
92. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 2007;13(7):2151–7.

93. Loos M, Giese NA, Kleeff J, Giese T, Gaida MM, Bergmann F, et al. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic cancer. Cancer Lett. 2008;268(1):98–109.
94. Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma. World J Surg. 2010;34(5):1059–65.
95. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010;33(8):828–33.
96. Le DT, Ko AH, Wainberg ZA, Picozzi VJ, Kindler HL, Wang-Gillam A, et al. Results from a phase 2b, randomized, multicenter study of gvax pancreas and CRS-207 compared to chemotherapy in adults with previously-treated metastatic pancreatic adenocarcinoma (eclipse study). J Clin Oncol (Meeting Abstracts). 2017;35(Suppl):345.
97. Le DT, Crocenzi TS, Uram JN, Lutz ER, Laheru DA, Sugar EA, et al. Randomized phase II study of the safety, efficacy, and immune response of GVAX pancreas vaccine (with cyclophosphamide) and CRS-207 with or without nivolumab in patients with previously treated metastatic pancreatic adenocarcinoma (stellar). J Clin Oncol (Meeting Abstracts). 2015;33(Suppl):abstract TPS4148.
98. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-pd-l1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–65.
99. Kim HJ, Kim MH, Myung SJ, Lim BC, Park ET, Yoo KS, et al. A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve. Am J Gastroenterol. 1999;94(7):1941–6.
100. Steinberg W. The clinical utility of the CA 19-9 tumor-associated antigen. Am J Gastroenterol. 1990;85(4):350–5.
101. Elebro J, Ben Dror L, Heby M, Nodin B, Jirstrom K, Eberhard J. Prognostic effect of hENT1, dCK and HuR expression by morphological type in periampullary adenocarcinoma, including pancreatic cancer. Acta Oncol. 2016;55(3):286–96.
102. Nordh S, Ansari D, Andersson R. Hent1 expression is predictive of gemcitabine outcome in pancreatic cancer: a systematic review. World J Gastroenterol. 2014;20(26):8482–90.
103. Gundewar C, Sasor A, Hilmersson KS, Andersson R, Ansari D. The role of sparc expression in pancreatic cancer progression and patient survival. Scand J Gastroenterol. 2015;50(9):1170–4.
104. Vaz J, Ansari D, Sasor A, Andersson R. Sparc: a potential prognostic and therapeutic target in pancreatic cancer. Pancreas. 2015;44(7):1024–35.
105. Cheng L, Li M, Hu J, Ren W, Xie L, Sun ZP, et al. UGT1A1∗6 polymorphisms are correlated with irinotecan-induced toxicity: a system review and meta-analysis in asians. Cancer Chemother Pharmacol. 2014;73(3):551–60.
106. Yang C, Liu Y, Xi WQ, Zhou CF, Jiang JL, Ma T, et al. Relationship between UGT1A1∗6/∗28 polymorphisms and severe toxicities in chinese patients with pancreatic or biliary tract cancer treated with irinotecan-containing regimens. Drug Des Devel Ther. 2015;9:3677–83.

Gastroenteropancreatic Neuroendocrine Tumors

16

George A. Fisher

Defining Gastroenteropancreatic Neuroendocrine Tumors

The field of neuroendocrine tumor (NET) research has been handicapped by the lack of adequate cell lines and murine models of the disease, as well as an evolving and at times confusing system of clinical classification. The term "carcinoid" itself has been ambiguous and in some tumor registries "carcinoids" were not included since they were considered "benign" unless there was specific mention in a pathology report referencing the tumor as "malignant." Embryologic classification of NETs as foregut, midgut, and hindgut was initially helpful in that each site of origin can have distinct clinical and biological properties, but this too has fallen out of favor.

The normal cells that give rise to NETs are endocrine cells, which are widely distributed throughout the gastrointestinal (GI) and pancreaticobiliary tract, yet comprise only ~1% of cells in the gut or pancreas. In the GI tract, these cells tend to occupy the intestinal crypts, while in the pancreas, they constitute the well-circumscribed nests known as islets of Langerhans. Hence, NETs arising from the pancreas have historically been referred to as "islet cell tumors." In 2010, the World Health Organization (WHO) categorized all NETs from the GI and pancreaticobiliary tracts as malignant tumors except for pancreatic neuroendocrine microadenomas. This designation ensured that NETs would be included in tumor registries.

These endocrine cells and the tumors that arise from them harbor secretory granules that contain peptide hormones, some of which are associated with specific syndromes and some which can be routinely measured in the blood as tumor markers. The type of peptides secreted can help identify the tissue of origin, though there is overlap. For example, serotonin is most closely associated with midgut tumors, primarily ileal, and only rarely is secreted by pancreatic tumors and virtually never associated with rectal neuroendocrine tumors. Similarly, pancreatic polypeptide, glucagon, and insulin are exclusively made by pancreatic NETs.

The preferred current classification system emphasizes the organ of origin, degree of differentiation and grade, the stage, and whether or not the tumor is associated with a functional syndrome. Note that this chapter will not address those GI malignancies described as "poorly differentiated carcinoma with neuroendocrine features" and "goblet cell carcinoids" and "mixed adeno-neuroendocrine carcinomas," each of which is more properly managed as one would an adenocarcinoma.

Epidemiology

Though considered rare in incidence (2–5 per 100,000) [1, 2], the prevalence of NET patients is greater than that of gastric, esophageal, and pancreas cancers combined [3, 4]. Furthermore, the incidence of NETs is increasing from 1.09 to 5.25 per 100,000 [4]. Probably much of this change can be attributed to an increase in utilization of cross-sectional imaging [5, 6] and endoscopies. The Netherlands Cancer Registry reported an increase in the incidence of high-grade gastroenteropancreatic (GEP) neuroendocrine carcinoma from 0.3 to 0.54 per 100 over the last two decades [7].

In an autopsy study over a 12-year period in a defined Swedish population, the incidence of gastroenteropancreatic (GEP) NETs was 199 among 16,294 necropsies (1.22%), while the clinically reported incidence in the same population was 44 in 250,000 (0.018%) [8]. The disparity in clinical versus autopsy incidence makes it clear that a subset of NETs are "incidentalomas," i.e, tumors that would have no clinical significance in the lifetime of the patient.

In a Surveillance, Epidemiology, and End Results (SEER) database report of 35,618 neuroendocrine tumors of all sites between 1973 and 2004, the age-adjusted incidence for non-pancreatic primaries was 4.7 per 100,000 patients

G. A. Fisher (✉)
Department of Medical Oncology, Stanford University School of Medicine, Stanford, CA, USA
e-mail: georgeaf@stanford.edu

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_16

[4]. Median age of diagnosis was 63 years with a slightly higher incidence in males than females (4.97 versus 4.49 per 100,000). A database study from a Swedish registry evaluated 5184 carcinoid tumors seen between 1958 and 1998 and reported somewhat lower incidence for men and women as 2.0 and 2.4 per 100,000, respectively [9].

The incidence of high-grade GEP neuroendocrine carcinoma is more difficult to ascertain due to the fact that various international cancer registries do not collect information on tumor grade. Nevertheless, the available data shows that high-grade GEP neuroendocrine carcinomas are rare. For example, data from the SEER demonstrate the incidence of colorectal neuroendocrine carcinoma as 0.2 per 100,000 patients, while estimates of annual incidence from the Netherlands Cancer Registry from 2000 to 2010 are higher at 0.54 per 100,000 patients [7, 10].

Various recent analyses have indicated that the incidence of NETs has been rising over time in the United States and elsewhere [3, 11]. In the SEER analysis mentioned above, there was a significant increase in the age-adjusted incidence for all NETs from 1.09 to 5.25 per 100,000 [4]. In Europe and Asia, the incidence appears lower and ranges from 1.1 to 3.24 cases per 100,000 [12, 13]. Similarly, high-grade neuroendocrine carcinoma incidence has been increasing.

This discrepancy between different countries may be due to older data and differences in data registration, as well as changes in the nomenclature and classification. But it also may reflect variability in environmental factors and tumorigenesis. Nevertheless, various publications have reported that the observed rise in NETs may be related to increased detection rates given the improvements in diagnostic imaging, particularly computed tomography (CT) and gastrointestinal endoscopy [6, 14]. This includes incidental identification of asymptomatic earlier stage lesions that may not have been revealed otherwise. In SEER database of carcinoid cases treated between 1973 and 1997, 55% of cases were gastrointestinal; of those small intestine carcinoids were 45%, most commonly in the ileum. Followed by 20% noted in the rectum, 16% in the appendix, 11% in the colon, and 7% in the stomach [15]. However, the SEER study of carcinoid patients between the years 1992 and 2008 found that more patients were diagnosed with rectal carcinoids than intestinal carcinoids, since the implementation of colonoscopy screening (approximately in the year 2000) [16].

Biology and Classification

The term carcinoid, "karzinoide" ("carcinoma-like"), was initially introduced in 1907 by Dr. Siegfried Oberndorfer to describe types of morphologically distinct benign small bowel lesions. In 1929, he amended his classification to include the possibility that these small bowel tumors may be malignant and may also metastasize [17].

More recently, the term "carcinoid" is generally applied to well-differentiated neuroendocrine tumors originating from various anatomic locations including: the digestive tract, lungs, or rare primary sites such as the kidneys or ovaries. The term carcinoid or NET implies well-differentiated histology. In contrast, the term neuroendocrine carcinoma has been adapted to describe high-grade or poorly differentiated neuroendocrine tumors. In the digestive system, well-differentiated neuroendocrine tumors of the luminal gastrointestinal tract have been designated carcinoid tumors or neuroendocrine tumors, while those arising in the pancreas have been termed pancreatic neuroendocrine tumors.

NETs arise from enterochromaffin (neuroendocrine) cells, which refer to the ability for these cells to stain with potassium chromate (chromaffin), a feature of cells that contain serotonin. Most NETs are relatively slow-growing neoplasms, but some do behave aggressively.

The classification and nomenclature of neuroendocrine neoplasms have historically focused on the site of origin from the embryonic divisions (foregut, midgut, or hindgut). Site-specific classifications vary in terminology as well as in histological grading and staging, which leads to morphologically similar neuroendocrine neoplasms being designated differently. However, features such as the proliferative rate and the extent of local spread are similar in all classifications. In general, midgut (distal small intestine and proximal colon) carcinoid tumors produce serotonin and other vasoactive substances that give rise to the typical carcinoid syndrome. However, tumors derived from the embryonic hindgut (distal colorectal) and foregut (gastroduodenum and bronchus) are rarely associated with a hormonal syndrome.

Foregut tumors include gastric and lung NETs. Gastric NETs are subdivided into three types with different biologic behaviors and prognoses. Type I is approximately 70–80% of all gastric NETs. It is more common in women and is associated with chronic atrophic gastritis and pernicious anemia [18]. The tumors arise form enterochromaffin-like cells and are usually less than 1 cm in size, often multiple, polypoid with a small central ulceration. They are rarely functional and often so indolent that they can be managed as a benign condition. Tumors less than 2 cm in size metastasize less than 10% of cases, while larger tumors seem to metastasize in approximately 20% of cases. Type II accounts for 5% of cases and is associated with gastrinomas (Zollinger-Ellison syndrome), usually as part of multiple endocrine neoplasia type I (MEN1). Similar to type II, they are considered indolent. Type III, on the other hand, is approximately 20% of all cases of gastric NETs. Unlike types I or II, they occur in the patient with normal fasting serum gastrin levels and absence of atrophic gastritis or the Zollinger-Ellison. They are aggressive with noted metastases in up to 65% of

patients. Lung NETs or bronchial carcinoids are classified among other pulmonary NETs such as small cell and large cell neuroendocrine lung cancer.

Midgut NETs include small bowel and appendix. Small bowel NETs are thought to originate from intraepithelial endocrine cell, whereas appendiceal NETs develop from subepithelial endocrine cells [19]. Small bowel NETs most commonly arise in the ileum, with approximately 25% of cases found to have more than 1 tumor noted at the time of diagnosis. Patients may be asymptomatic and diagnosed incidentally due to other presentation. Abdominal pain is the most common symptom in patients with small bowel NETs, occurring in roughly 40% of cases. The underlying cause of the pain may be secondary to small bowel obstruction, intussusception, mechanical effect, or mesenteric ischemia [20]. Metastatic disease to lymph nodes or the liver is common, and most patients with small bowel primary NETs and liver metastases have carcinoid syndrome.

Appendiceal NETs are usually asymptomatic, occurring in patients 40–50 years of age. They develop from subepithelial endocrine cells in the distal one-third of the appendix, where they are unlikely to cause obstruction. The presence of metastatic disease depends in large part on tumor size; tumors less than 2 cm in diameter have a low likelihood of metastases, whereas 30% of larger tumors have already metastasized at diagnosis [21].

Hindgut tumors include the colon and rectum NETs. Colon NETs are rarely functional tumors; most are asymptomatic and usually are diagnosed during evaluation for abdominal pain, diarrhea, or weight loss. Symptomatic patients present with significantly large tumors. The majority of tumors are located in the right colon, mainly in the cecum [22]; local nodal or distant metastases are found in 30% of cases. Similarly, the majority of rectal NETs are asymptomatic and found incidentally for other reasons. Most cases are localized at time of diagnosis, but as with other NETs, metastatic disease correlates with tumor size. Tumors less than 1 cm in size rarely metastasize, whereas those over 2 cm metastasize to the liver in 25% of cases [23]. Other poor prognostic features include deep invasion, lymphovascular invasion, and a high mitotic rate.

Poorly differentiated neuroendocrine carcinomas are aggressive, with a natural history that is characterized by early, widespread metastases. Thus, most patients have metastatic disease at the time of presentation. These tumors show similarities in morphology and biologic behavior to small cell lung cancer and large cell neuroendocrine lung cancer [24]. The majority of poorly differentiated neuroendocrine carcinomas are non-secretory. Their presentation is variable, depending on the site of the primary tumor and whether or not metastatic disease is present. Symptoms may be nonspecific such as fatigue, anorexia, and weight loss, or more specific including pain, nausea, emesis, dysphasia, jaundice, melena, hematochezia, or bowel obstruction [25].

Histological grade and differentiation of NETs correlate closely with clinical behavior. Grade refers to the proliferative activity that is commonly measured by the mitotic rate—number of mitotic figures per 10 high-powered fields (HPF)—or the Ki-67 index. In contrast, differentiation refers to the extent to which neoplastic cells resemble their original cell [26].

The World Health Organization (WHO) and the European Neuroendocrine Tumor Society (ENETS) differentiate 2 broad subgroups of NETs of the digestive track: well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas. Well-differentiated neuroendocrine tumors are further subdivided into low-grade and intermediate-grade according to proliferative rate (Tables 16.1 and 16.2 [27]). However, intermediate-grade carcinoid tumors that rise in the lung, but not in any other organ system, are referred to as atypical carcinoids. In general, these tumors follow a more indolent course. Poorly differentiated

Table 16.1 ENETS/WHO nomenclature and classification for NETs

Differentiation	Grade	Mitotic count[a]	Ki-67 index[b]	Traditional	ENETS, WHO
Well-differentiated	Low grade (G1)	<2 per 10 HPF	≤2%	Carcinoid, islet cell, pancreatic NET	NET, Grade 1
	Intermediate grade (G2)	2–20 per 10 HPF	3–20%	Carcinoid, atypical carcinoid[c], islet cell, pancreatic NET	NET, Grade 2
Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20%	Small cell carcinoma	Neuroendocrine carcinoma, Grade 3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, Grade 3, large cell

ENETS European Neuroendocrine Tumor Society, *WHO* World Health Organization

[a]Counted in 10 high-powered fields (HPF). 10 HPF = 2 mm^2, at least 50 fields (at 400× magnification) evaluated in areas of highest mitotic density. Cutoffs per American Joint Commission on Cancer Staging Manual, 8th edition

[b]Ki-67 index as assessed by MIB1 antibody staining: percent positive after count of 2000 cells in area of highest nuclear labeling. Cutoffs per American Joint Commission on Cancer Staging Manual, 8th edition

[c]The term "atypical carcinoid" only applies to intermediate-grade NETs of the lung

Table 16.2 Nomenclature and classification for NETs

Differentiation	Well-differentiated		Poorly differentiated
Grade	Low grade (G1)	Intermediate grade (G2)	High grade (G3)
Mitotic count[a]	<2 per 10 HPF	2–20 per 10 HPF	>20 per 10 HPF
Ki-67 index[b]	≤2%	3–20%	>20%
ENETS, WHO	NET, Grade 1	NET, Grade 2	Neuroendocrine carcinoma, Grade 3
Clinical course	Indolent	Intermediate	Rapid
Mutation[c]	DAXX/ATRX		TP53, RB1

ENETS European Neuroendocrine Tumor Society, *WHO* World Health Organization
[a]Counted in 10 high-powered fields (HPF). 10 HPF = 2 mm^2, at least 50 fields (at 400× magnification) evaluated in areas of highest mitotic density. Cutoffs per American Joint Commission on Cancer Staging Manual, 8th edition
[b]Ki-67 index as assessed by MIB1 antibody staining: percent positive after count of 2000 cells in area of highest nuclear labeling. Cutoffs per American Joint Commission on Cancer Staging Manual, 8th edition
[c]See reference [27]

Table 16.3 Inherited disorders associated with pancreatobiliary neuroendocrine tumors

Tuberous sclerosis	9q31.13, 16p13.3	TSC1/Hamartin, TSC2/ Tuberin	Insulin and somatostatin producing pancreatic NETs	Hamartomatous polyp

neuroendocrine carcinomas are high-grade carcinomas that resemble small cell or large cell neuroendocrine carcinoma of the lung and are often associated with aggressive form of disease [28]. Both small and large cell tumors grow in sheets, forming nest-like structures with necrotic centers [29].

As was mentioned, the 2010 WHO classification of NETs depends widely on the proliferative rate of the specific tumor. This rate is assessed by mitotic counts or Ki-67 index, thus distinguishing between low-, intermediate-, and high-grade tumors (Table 16.1). The cutoff of 2/10 HPF to stratify low-grade disease versus 20/10 HPF for poorly differentiated gastroenteropancreatic neuroendocrine has been well supported in various studies of different NETs [30, 31]. Similarly with Ki-67, the ENETS, American Joint Committee on Cancer (AJCC), and the 2010 WHO classification include a cutoff of less than 3% to define low-grade, 3–20% for intermediate-grade, and more than 20% for high-grade NETs [26]. In addition, morphological features of poorly differentiated neuroendocrine carcinomas are often suggestive of the diagnosis [32].

In several cases of poorly differentiated neuroendocrine carcinomas, non-neuroendocrine components may be noted in the tumors. These components may include adenocarcinoma, signet ring cell carcinoma, and, more rarely, squamous cell cancer. Tumors that contain both neuroendocrine and non-neuroendocrine components, each of which represents at least 30% of the lesions, are defined by the 2010 WHO classification as mixed adenoneuroendocrine carcinomas. On the other hand, tumors that contain less than 30% neuroendocrine carcinoma are classified as adenocarcinoma with neuroendocrine differentiation.

NETs' staging is a tumor-node-metastasis (TNM)-based system that has been endorsed by the WHO and adapted by the AJCC and ENETS. The system includes separate TNM staging of the appendix, colorectal pancreas, small bowel/ampulla of vater, and stomach primary sites. Nevertheless, some differences continue to exist between the AJCC and ENETS TNM systems. These include some differences in T-stage definition: ENETS proposes to stage poorly differentiated neuroendocrine carcinoma in the same way as well-differentiated NETs, whereas the AJCC stages poorly differentiated neuroendocrine carcinomas as adenocarcinomas. Nevertheless, several studies supported the prognostic validity of both TNM stage and proliferative rate using this new system in luminal GI tract and pancreatic NETs [33–36].

Lastly, NETs are also classified based on functionality and the presence of clinical symptoms as results of excess hormonal secretion by the tumor. The classification is based on the predominant hormone produced and the resulting clinical syndrome associated with it. For example, if a tumor is noted to produce gastrin but no associated symptoms of the Zollinger-Ellison syndrome, then it would be appropriate to use the term "gastrin-secreting NET" and not gastrinoma. Other classifications of pancreatic NETs include insulinoma (insulin), gastrinoma (gastrin), glucagonoma (glucagon), VIPoma (vasoactive intestinal polypeptide), or somatostatinoma (somatostatin) (Table 16.3). Likewise, carcinoid tumors are classified similarly whether they produce symptoms of the carcinoid syndrome or not.

Syndromes

The term "carcinoid syndrome" applies to a constellation of symptoms that are mediated by various vasoactive factors produced by some carcinoid tumors. The typical carcinoid syndrome occurs predominantly in patients with metastatic carcinoid tumors, and consists primarily of flushing and diarrhea. Typically, these tumors originate in the midgut, in contrast to tumors that originate from the hindgut and foregut, which rarely produce the carcinoid syndrome.

NETs synthesize, store, and release a variety of polypeptides, prostaglandins, and biogenic amines. Some of these substances are responsible for the carcinoid syndrome, but the relative contributions and specificity of any particular components are unclear. Furthermore, the liver is capable of inactivating some of these bioactive products that are secreted into the portal circulation. This may explain why vasoactive products secreted by gastrointestinal carcinoid tumors with hepatic metastases, directly into the systemic circulation, typically develop carcinoid syndrome [37]. Multiple secretory polypeptides and amines have been identified; most notable are serotonin, histamine, tachykinins, kallikrein, and prostaglandins.

Serotonin is derived from tryptophan in enterochromaffin cells of the GI tract, where it is used to regulate intestinal motility and absorption. Serotonin is also found in the central nervous system (CNS) where it regulates mood, appetite, and sleep; and is found in platelets, where it serves as a vasoconstrictor. Serotonin is metabolized to 5-hydroxyindoleacetic acid (HIAA) by aromatic amino acid decarboxylase. Patients with carcinoid syndrome have significant increase in tryptophan metabolism and increase in production of serotonin, thus causing diarrhea. In addition, serotonin stimulates fibroblast growth and fibrogenesis, which may lead to cardiac valvular fibrosis. Lastly, diversion of tryptophan metabolism to primary serotonin production results in niacin deficiency, decreased protein synthesis, and hypoalbuminemia [38].

Foregut carcinoids such as gastric and bronchial lack the aromatic amino acid decarboxylase that converts 5-hydroxytryptophan to serotonin. These tumors produce 5-hydroxytryptophan and histamine instead of serotonin. These patients suffer from atypical flushing and pruritus. Other polypeptides include kallikrein, which is a potent vasodilator responsible for flushing and stimulation of intestinal motility [39]. Tachykinins including substance P, neurokinin A, and neuropeptide K may contribute to flushing and diarrhea [40].

Patients with carcinoid syndrome present with various symptoms; the majority presenting with flushing primarily involving the face, neck, and upper chest. In some cases, severe flushing may be associated with episodes of decreased blood pressure and rise in pulse rate. Most episodes occur spontaneously, but they can be provoked by such activities as eating, drinking alcohol, and defecation; others are aggravated by emotional events, or medications such as anesthesia. The episodes last between 30 seconds and 30 minutes, but as the disease progresses, the episodes may last longer and the flushing may become more diffuse [41].

Diarrhea occurs in approximately 80% of patients, with episodes ranging from a couple of episodes to debilitating high numbers per day. The stools are typically watery and non-bloody, but can be explosive. They are usually accompanied by abdominal cramping and are unrelated to flushing episodes [42].

Other manifestations of the carcinoid syndrome include cardiac valvular lesions, characterized by pathognomonic plaque-like deposits of fibrous tissue. The right side of the heart is most often affected. Various bioactive substances are inactivated by the lung, thus protecting the left heart. Bronchospasm, which occurs in about 20% of patients, usually manifests during flushing episodes. It is imperative not to mistake carcinoid wheezing for bronchial asthma because treatment with beta agonists may trigger intense, prolonged vasodilation. Other presentations include: pellagra, due to the lack of niacin production; muscle wasting that may occur because of poor protein synthesis; and Peyronie's disease as a result of extensive fibrosis can occur in the retroperitoneal area [43, 44].

Carcinoid crisis is a term that represents a life-threatening form of carcinoid syndrome. Carcinoid crisis occurs due to the release of an overwhelming amount of biologically active substances from the NETs that is prompted by tumor manipulation at time of biopsy or surgery or by anesthesia [45]. Less common, carcinoid crisis may occur after chemotherapy, hepatic artery embolization, or radionuclide therapy, mostly in patients with extensive tumor bulk [46, 47].

Diagnosis

Patients with NETs present with various signs and symptoms including: chronic flushing and/or diarrhea due to carcinoid syndrome; chronic and/or recurrent abdominal pain, which may be caused by bowel obstruction; right upper quadrant pain, hepatomegaly, and early satiety because of liver metastasis; or as an incidental finding during endoscopic procedures or surgeries for other indications.

Biochemical Testing

Patients with concerning presentation for NETs may be screened initially with biochemical testing. This includes evaluation of 5-hydroxyindoleacetic acid (5-HIAA), which is the end metabolite of serotonin metabolism. Other biochemical tests are available, but due to relatively low sensitivity and specificity, these tests are not indicated as initial screening methods.

Serotonin is metabolized mainly to 5-HIAA, which is excreted by the kidneys. The normal rate of 5-HIAA excretion ranges from 2 to 8 mg/day; values that are up to 30 mg/day may be due to malabsorption syndromes such as celiac and Whipple's disease, or after the ingestion of large amounts of tryptophan- or serotonin-rich foods. Patients with NETs may have urinary 5-HIAA levels that are as low as 30 mg/day, but they may also have levels higher than 100 mg/day [48].

Urinary 5-HIAA testing is 90% sensitive and specific for carcinoid syndrome [48]. However, urinary 5-HIAA is less sensitive for patients without carcinoid syndrome; further, various drugs as well as tryptophan or serotonin-rich foods may cause false-positive results. Patients should avoid intake of tryptophan- and serotonin-rich foods as well as medicines that may cause a false-positive urinary 5-HIAA at least 24 hours prior and during urine collection.

As was mentioned, primary midgut NETs produce the highest levels of serotonin and, thus, may be most specific for evaluation by urinary 5-HIAA. Foregut and hindgut lack the enzyme aromatic amino acid decarboxylase, and therefore cannot convert 5-hydroxytryptophan (5-HT) to serotonin. These tumors have by default low levels of 5-HIAA, but they have high levels of 5-hydroxytryptophan and histamine.

Chromogranins are a family of regulatory neuroendocrine proteins that are found in dense-core secretory vesicles, produced by chromaffin cells of the adrenal medulla, paraganglia, and beta cells of the pancreas. Elevated levels of chromogranin A (CgA) have been associated with well-differentiated NETs more than other granins. In addition, increasing blood concentration of CgA is indicative of larger tumor burden [49, 50].

CgA secretion varies on a daily basis and is affected by food intake and medications, especially proton pump inhibitors [51, 52]. Its use as a screening test for the diagnosis of NETs has been refuted given relatively low specificity of the test. In a study comparing patients with well-differentiated NETs, chronic atrophic gastritis, and healthy individuals [50], it was noted that when a cutoff range of 84–87 U/L was used, the sensitivity was only 55%; but with a cutoff range of 31–32 U/L, the sensitivity and specificity were 75% and 84%, respectively. Therefore, it is more appropriate to use CgA testing as a tumor marker for patients with an established diagnosis as means to assess disease progression, response to therapy, or recurrence after surgical resection.

Similarly, serotonin testing has been described in the literature, but the sensitivities and specificities of many of these tests have not been well established. Furthermore, serotonin may be released due to platelet activation by ingestion of tryptophan- or serotonin-rich foods, which may result in false-positive results.

Other markers, including alpha-fetoprotein and human chorionic gonadotropin, are found elevated in some patients with NETs, but the utility of such markers has not been verified [53].

Imaging

Biochemical testing requires active secretory NETs, which may or may not result in carcinoid syndrome. Bioactive products that are excreted by NETs of the small intestine are inactivated in the portal circulation, rendering urinary and blood testing ineffective. Various imaging modalities are employed for diagnosis and surveillance of NETs including computed tomography (CT), magnetic resonance imaging (MRI), and somatostatin receptor scintigraphy (octreoscan).

Computed tomography is noninvasive and a readily available imaging modality that may be utilized as the primary imaging method to identify carcinoid tumors. For patient with NETs, spiral multiphasic contrast-enhanced CT is recommended, as it maximizes the conspicuity of liver metastases compared with normal liver parenchyma. Because most NETs are highly vascular, they are enhanced with iodinated contrast in the early arterial phase and washout during the portal venous phase [54].

The classic finding on CT scan is a mesenteric desmoplastic fibrosis that appears as a mass-like soft tissue ("*cauliflower*-like") with extensions into the mesenteric fat toward the small bowel resulting in retraction of the bowel. The mass-like soft tissue may or may not be calcified and is usually associated with small intestinal NETs, which is likely caused by direct extension of primary tumors into the mesentery or due to mesenteric lymph node metastases.

However, the ability of CT scan to detect NETs is limited. Approximately 6–20% of NETs are hypovascular and would not be easily detected. In addition, CT scan is inadequate in identifying small size tumors such as those originating from the jejunum and ileum, nor is it able to differentiate colonic NETs from the more common adenocarcinoma [54].

Magnetic resonance imaging is the most sensitive in detecting liver metastases. Unlike the spiral multiphasic contrast-enhanced CT scans, lesions can be visualized without contrast in T1- and T2-weighted sequences, thus decreasing the variability noted with CT scans. In a study evaluating 64 patients with metastatic gastrointestinal NETs, multiphasic MRI was able to detect more liver metastasis than either CT scans or octreoscan [55]. However, MRI similar to CT scan is also limited by tumor size.

Somatostatin receptor scintigraphy (octreoscan) takes advantage of the highly expressed somatostatin receptors on NETs as a mean to detect metastatic disease in the whole body. The technique uses a radiolabeled form of the somatostatin analog octreotide (11-indium pentetreotide) to highlight tumor cells. Older studies reported favorable results of octreoscan as compared to other imaging modalities [56]. However, over the past several decades, various technological advancements to CT and MRI scans may have cast a doubt on its importance in the staging of NETs. The addition of single-photon emission computed tomography (SPECT) has improved the accuracy of octreoscan to differentiation between areas of physiologic and pathologic uptake. Furthermore, baseline octreoscan may be useful as it may predict clinical response to therapy with somatostatin analogs.

Nevertheless, octreoscan-SPECT accuracy continues to be less than that of CT and MRI as demonstrated in a series of 121 patients with a GEP-NET [57], where only 79% of patients had abnormal findings on octreoscan that correlated with the abnormalities noted on cross-sectional imaging. In addition, there were no soft tissue abnormalities identified by octreoscan-SPECT that were not illustrated on cross-sectional imaging. Lastly, octreoscan use is also limited by the expression level of somatostatin receptor. Low-expressing somatostatin receptor tumors such as poorly differentiated NETs are unlikely to be detected on octreoscan imaging.

The guidelines for the use of octreoscan are not consistent; the North American Neuroendocrine Tumor Society suggests its use as baseline assessment and to repeat nuclear imaging as clinically indicated; the National Comprehensive Cancer Network (NCCN) indicates its use as "appropriate"; and the European Neuroendocrine Tumor Society proposes its use for assessing secondary sites of disease [58–60].

Functional positron emission tomography imaging is a technique that utilizes tracers for functional imaging—18-F-dihydroxy-phenyl-alanine (18F-DOPA), 11-C-5-hydroxytryptophan(11-C-5-HTP),and68-Ga-DOTA-D-Phe^{1}-Tyr^{3}-octreotide (68-Ga-DOTATOC)—which combines high-resolution PET integrated with CT. These modalities provide higher spatial resolution with improved sensitivity for small lesions. In recent studies comparing integrated PET/CT with octreoscan, octreoscan-SPECT, or CT scan alone, PET/CT demonstrated superior sensitivity as compared to the other modalities [61, 62].

Management

In general, evaluation and management of patients with NETs includes: radiographic staging and tumor localization; pathologic assessment of tumor differentiation and grade; surgically resection of the tumor, even if liver metastases are present; control of carcinoid symptoms; antitumor therapy for unresectable metastatic disease; and surveillance.

Radiographic staging and tumor localization are assessed with various imaging modalities as was previously discussed. Evaluation of patients with metastatic carcinoid with an unknown primary should include an upper and lower endoscopy, with attention to the terminal ileum. CT enterography may serve as an alternative modality for this purpose; however, video capsule endoscopy is not recommended given the risk of capsule retention and bowel obstruction at the site of disease. Patients with rectal carcinoids may be evaluated with transrectal endoscopic ultrasound (TEUS) to assess for tumor size, depth of invasion, and lymph node involvement.

The primary treatment for patients with non-metastatic NETs is surgery. The scope of surgery depends on the site of origin and size of primary tumor. In patients with metastatic disease, surgery provides prolonged control of symptoms and tumor growth. To that end, metastasectomy is commonly favored over medical therapy if, potentially, resection of liver metastases is feasible.

Patients with unresectable disease, or those who continue to be symptomatic despite resection, are considered for systemic therapy. At present, the treatment for patients with low-grade (G1) and intermediate-grade (G2) gastroenteropancreatic NETs is the same, even though intermediate-grade tumors have slightly worse prognosis than low-grade tumors [26]. Poorly differentiated NETs are high-grade (G3) carcinomas, with a rapid progressive clinical course and a poor prognosis, that are generally treated with platinum-based chemotherapy regimens similar to small cell lung carcinoma. Symptomatic patients from bioactive disease are treated specifically depending on the underlying syndrome. For example, carcinoid syndrome is initially treated with somatostatin analogs, whereas patients with insulinomas are treated with carbohydrates and diazoxide that inhibit the release of insulin. For those with gastrinoma, high doses of oral proton pump inhibitors are considered the initial treatment of choice.

Surgical Considerations in the Management of Gastrointestinal and Pancreatic Neuroendocrine Tumors

Surgical resection of the primary tumor and of resectable metastatic disease is the cornerstone of therapy for NETs. However, in some unique situations, surveillance rather than immediate surgery may be the preferred approach. For example, the optimal management of *small, asymptomatic, well-differentiated pancreatic NETs* remains controversial. Certainly, surgical resection for these tumors has traditionally been associated with excellent survival outcomes [63]. However, some investigators have recently questioned the need for upfront surgical resection in this clinical situation, and have proposed radiographic surveillance as a suitable alternative strategy. A recent retrospective, single-institution, matched case-control study of 181 patients with sporadic, small (<3 cm), stage I–II pancreatic NETs [64] compared 104 patients who were selected for observation and 77 patients who underwent resection. At a median follow-up of 44 months for the patients in the observation group, the median tumor size had not changed and no patient had developed evidence of metastases. Within the resection group, 6% of patients developed recurrence at a median of 5.1 years, but no patient in either group died of disease. In contrast, an analysis of 380 patients with small (≤2 cm) pancreatic NETs from the National Cancer Database [65] showed a significant survival advantage for the 81% of patients who underwent resection as opposed to the 19% of patients who

underwent observation (5-year, 82% vs. 34%, $P < 0.0001$). This difference persisted in multivariate analysis controlling for age, tumor size, grade, margin status, and nodal metastasis. It should be noted that this study included patients with grade 3 tumors. An additional consideration, which may influence decision-making in this clinical situation, is that the incidence of nodal metastasis in pancreatic NETs is proportional to the size of the primary tumor size: typically 0% for tumors <1 cm, up to 20% for tumors 1–2 cm, and 30–40% for tumors 2–3 cm [66]. Taken together, these data support the notion that the decision to proceed with surgical resection of a small, asymptomatic pancreatic NET should be individualized and carefully considered based on the extent of the operation required (pancreaticoduodenectomy versus distal pancreatectomy, which can typically be performed laparoscopically), the size of the tumor, and the age and comorbidities of the patient. Certainly, there is growing literature to support a surveillance strategy for small nonfunctional tumors, in the head of the pancreas, especially in older patients.

Another situation where surgery may be initially deferred is patients with small, nonfunctional, pancreatic NETs in the setting of *MEN-1 syndrome*. MEN-1 patients tend to have multifocal NETs involving the entire gland, and a parenchyma-sparing approach is preferable, as the chance of leaving residual small tumors in the pancreatic remnant after a partial pancreatectomy is significant. On the other hand, if left in situ, pancreatic NETs could metastasize to the liver and lead to the patient's death. A prospective study from the NIH [67] has recommended surgical resection for MEN-1 patients whose pancreatic NETs are larger than 2.5 cm, as this size threshold was identified as predictive of the development of liver metastases.

Along the same lines, a more conservative approach can be employed for *type I and II gastric carcinoids*. In contrast to type III gastric carcinoids, which are sporadic, solitary, bulky, and with significant metastatic potential, typically requiring surgical resection, type I and II gastric carcinoids are usually small and multifocal involving the entirety of the stomach, in the setting of hypergastrinemia. The root of the problem is pernicious anemia and atrophic gastritis in type I patients [68] and Zollinger-Ellison Syndrome in type II patients [69]. Diagnosis is usually established by high gastrin levels, positive anti-parietal cell antibodies and achlorhydria in type I tumors, high gastrin levels and decreased gastric PH in type II tumors, and normal gastrin levels in type III tumors. Type I and II patients should be treated with annual endoscopic surveillance and endoscopic resection of small tumors as they appear. There is a small risk of concomitant adenocarcinoma with type I gastric carcinoid, which may prompt formal surgical resection. The role of antrectomy in type I patients as a way to interrupt the vicious cycle of hypergastrinemia remains controversial, as annual endoscopic polypectomy will suffice in the majority of cases. On the contrary, resection of the gastrinoma in type II patients is expected to address the root of the problem and is strongly recommended.

In the case of *small bowel NETs*, resection is routinely advised, regardless of size or the presence of metastases, to prevent the development of complications from the primary tumor, such as bowel obstruction or venous intestinal ischemia due to the associated desmoplastic reaction in the mesentery. Surgeons experienced in the management of these tumors are familiar with 5 specific issues unique to this situation. First, a *prophylactic cholecystectomy* should be performed as postoperative octreotide therapy may lead to cholelithiasis and cholecystitis [70]. Second, in up to 30% of cases, these tumors can be *multifocal*, typically along the ileum, so the entire length of the small intestine should be carefully examined and palpated intraoperatively, so all tumors are found and included in the resection [71]. Third, lymph node metastases can track along the ileocolic pedicle all the way up to its origin at the level of the duodenum, and this entire lymph node-bearing area should be included in the resection. Metastatic lymph nodes in this setting are easily palpable as they can lead to significant *cicatrization (scarring) and shortening of the mesentery*. This mesenteric fibrosis, however, can make dissection difficult, and particular attention is required to preserve the vascular supply of adequate length of the remaining intestine [72]. Fourth, surgeons and anesthesiologists should be familiar with and anticipate the possibility of *carcinoid crisis*. This can be precipitated by stressful situations (such as induction of anesthesia) and can manifest as flushing, bronchospasm, and cardiovascular abnormalities, such as tachycardia, arrhythmias, and hypotension, which may not respond to conventional resuscitation methods. Carcinoid crisis usually develops in patients with previous carcinoid syndrome but can be encountered even in patients without it—but with bulky metastatic disease in an area draining into the systemic and not the portal circulation (such as liver metastases, large retroperitoneal nodal metastasis, ovarian metastasis). Although vasopressors can be used to address carcinoid crisis if it develops, it is most optimal to prevent carcinoid crisis through the prophylactic administration of preoperative octreotide bolus (typically 200 mcg IV) right before induction of anesthesia, sometimes followed by an octreotide continuous infusion intraoperatively if extensive metastatic disease in the aforementioned areas is present [73]. Last, in patients with long-standing carcinoid syndrome, preoperative evaluation with an echocardiogram is helpful to identify any changes related to *carcinoid heart disease*, typically manifesting as endocardial thickening of the right heart valves [74].

Liver failure due to replacement by tumor is the most common cause of death in NET patients. Therefore, an aggressive surgical approach to completely resect (or sometimes

cytoreduce) *NET liver metastases* has been traditionally recommended. In an international registry of 339 such patients, this surgical strategy was associated with a 74% 5-year and a 51% 10-year survival probability. However, intrahepatic recurrence was almost universal at 5 years, supporting the notion that this approach is a way to "reset the clock" for these patients [75]. For patients who are not candidates for surgery, hepatic artery embolization (bland, chemo-, or radio-embolization) can be utilized as NET liver metastases are typically hypervascular and receive their blood supply from hepatic artery branches. Intra-arterial therapy can be associated with improved hormonal symptom control and/or long-term survival in this setting. In a multi-institutional database of 414 such patients, a 30% 5-year survival was noted after hepatic artery therapies [76]. Liver transplantation has been advocated in selected patients with bilateral unresectable symptomatic liver NET metastases [77]. Although until now the role of liver transplantation in this setting had been considered at best investigational, a recent report from the National Cancer Institute of Milan has shown very promising results (89% 10-year survival) in 42 patients who met restrictive criteria (age < 60, low-grade histology G1 or G2, prior removal of primary tumor drained by the portal vain, prior removal of any extrahepatic disease, involvement of <50% of the liver by metastasis, and stable disease/response to therapies for at least 6 months before transplant consideration) [78].

Systemic Therapies

Well-Differentiated Gastrointestinal and Pancreatic Neuroendocrine Tumors

Gastrointestinal and pancreatic NETs may have similar characteristics on routine histologic evaluation, but they have a different pathogenesis and biology (Table 16.3) [79]. Pancreatic NETs have a worse prognosis than carcinoid tumors [80] and respond differently to anticancer agents, with most agents demonstrating higher response rates among patients with pancreatic NETs than in those with carcinoid.

Somatostatin Analogs (SSAs)

Somatostatin, also known as growth hormone-inhibiting hormone (GHIH), is produced by paracrine cells throughout the gastrointestinal tract and inhibits gastrointestinal endocrine secretion. Somatostatin receptor is a typical G protein-coupled receptor with 5 known subtypes that are highly expressed on gastrointestinal NETs [81]. The expression of somatostatin receptors can be evaluated by octreoscan, which uses a radiolabeled form of the somatostatin analog octreotide: indium-111 (111-In) pentetreotide.

Somatostatin analogs, which target somatostatin receptor (SSTR)-2 and SSTR-5, are considered to be the initial treatment option for patients with unresectable symptomatic gastrointestinal NETs. Asymptomatic patients with limited tumor burden are generally observed. However, somatostatin analog should be initiated for patients with high tumor burden or if tumor progression is documented after an observation period. A trial of somatostatin analog may also be considered in patients with negative octreoscan, given that a negative or a positive scan result does not necessarily correlate with responses or duration of disease control in some cases, such as carcinoid syndrome and miliary disease spread [82]. Nevertheless, resection continues to be preferred over medical therapy for those who are amendable to surgery.

Various studies investigating gastroenteropancreatic NETs and functional pancreatic NETs have demonstrated the effectiveness of somatostatin analogs in controlling the symptoms associated with carcinoid syndrome. Control of flushing and/or diarrhea was reported in approximately 50–90% of patients, and reduction in 5-HIAA levels was roughly 60–70% [83–87].

Furthermore, somatostatin analogs are effective in controlling symptoms associated with functioning pancreatic NETs such as VIPomas (diarrhea) and glucagonomas (rash). However, they are less effective at controlling hormone-related symptoms of insulinomas and gastrinomas. Somatostatin analogs may actually worsen hypoglycemia symptoms in patients with insulinomas, due to inhibition of glucagon secretion.

In addition to symptomatic control, somatostatin analogs have been shown to control tumor growth. Various studies evaluating patients with NETs have shown prolonged periods of stability and progression-free survival (PFS), and in less than 10% of the cases, objective tumor shrinkage was reported [88–90]. This benefit was demonstrated in patients with functionally active and inactive tumors. The PROMID trial randomized 85 patients with unresectable metastatic small bowel gastrointestinal NETs to Sandostatin LAR 30 mg monthly or placebo. The treatment group time to progression was 14.3 months, which is significantly longer than the 6 months in the placebo group [88]. The CLARINET trial was a randomized, placebo-controlled phase III trial evaluating the antiproliferative effects of lanreotide in 204 patients with advanced well-differentiated or moderately differentiated, non-functioning gastroenteropancreatic NETs. The primary endpoint was PFS as determined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The study demonstrated that at the 2-year time point, PFS was not reached in the treatment group, whereas in the placebo arm, median PFS was 18 months (hazard ratio [HR] for progression or death 0.47; 95% CI, 0.30–0.73). The estimated rates of PFS at 2 years were 65.1% (95% CI, 54.0–74.1) in the lanreotide group and 33.0% (95% CI, 23.0–43.3) in the

Table 16.4 Comparative trials with somatostatin analogs

Study	Type	Tumor	Regimen	*N*	RR (%)	PFS (mo)	OS (mo)
Rinke et al. [88] (PROMID)	Randomized	Carcinoid	Octr Placebo	85	2	14.3 6	
Caplin et al. [91] (CLARINET)	Randomized	PENT carcinoid	Lanr Placebo	101 103	NR NR	Not reached 18	

Lanr Lanreotide, *NR* not reported, *PENT* pancreatic neuroendocrine tumor; *PFS* progression-free survival, *RR* response rate, *Octr* octreotide, OS overall survival

placebo group. There were no differences in quality of life or overall survival [91] (Table 16.4 [88, 91]).

Currently, there are 2 approved somatostatin analogs: octreotide and lanreotide, which are available in short- and long-acting formulations. Symptomatic patients may initially start with a short-acting octreotide and then transition to the long-acting formulation with dose titration to optimal symptom control. Sustained release formulations (depot preparation), octreotide LAR is a once-monthly injection that is now considered that standard of care [60, 92]. Typically, the initial dose is octreotide LAR 20 mg intramuscularly monthly; this dose may be escalated up to 60 mg monthly for optimal symptom control. However, the efficacy of doses higher than 30 mg monthly has not been prospectively established [93], and doses higher than 60 mg monthly appear to be associated with minimal marginal benefit [94].

Lanreotide is another long-acting somatostatin analog approved for the treatment of NETs. It appears to have similar clinical efficacy to octreotide [95]. Sustained release formulation of lanreotide is administered once monthly as a deep subcutaneous injection at doses ranging from 60 to 120 mg every 4 weeks.

Patients, who experience worsening symptoms toward the 4th week of each treatment cycle, may consider adding a short-acting octreotide for breakthrough symptoms, or increasing the frequency of administration of the sustained release formulation from the usual 4 weeks to 3 weeks. Of note, systemic therapeutic levels of octreotide may take 10–14 days after the initiation of the LAR injection.

Somatostatin analogs are usually well tolerated; nausea, abdominal discomfort, bloating, loose stools, and fat malabsorption are observed in approximately a third of patients—usually within the first weeks of treatment. Minor glucose intolerance may arise due to transient inhibition of insulin secretion. Approximately 25% of patients may develop asymptomatic gallstones or sludge due to reduced postprandial gallbladder contractility and delayed emptying [58, 60].

Interferon Alpha

Patients with advanced NETs have been treated with interferon alpha (IFNa) for many decades, but its use has been limited by the severity of the side effects including fatigue, myelosuppression, depression, influenza-like symptoms, weight loss, and changes of thyroid function. The European Neuroendocrine Tumor Society (ENETS) and the North American Neuroendocrine Tumor Society (NANETS) guidelines specify the use of IFNa as a second-line therapy for functioning gastrointestinal NETs after failure of somatostatin analog; whereas the NCCN guidelines indicate its use in patients with progressive metastases for whom there are no other treatment options.

IFNa use has focused on symptomatic control in patients with active secretory NETs. In a retrospective series, low-dose IFNa reduced the symptoms of hormonal hypersecretion in 40–70% of patients with gastrointestinal NETs and stabilized tumor growth in 20–40% [96–98].

IFNa doses range from 3 to 9 million units (MU) subcutaneously from 3 to 7 times per week with a usual dose of 3 to 5 MU/3 times weekly, due to the significant side effects associated with the treatment. Pegylated IFN 80 to 150 mcg per week subcutaneously may be considered given its better tolerance, but the data of its use are limited, and it is not approved for this indication [99]. The combination of INFa with somatostatin analogs has been evaluated in the literature, but the results have been inconsistent.

Molecular Targets

The current understanding of the molecular pathogenesis of NETs has shifted the treatment approach in recent years by specifically targeting tumor angiogenesis and using it as a main focus of many of the current therapies. NETs are highly vascular tumors that express several cellular growth factors and their receptors, including vascular endothelial growth factor (VEGF) and the VEGF receptor (VEGFR). Many of these cellular growth factors receptors function as tyrosine kinases (TKs) that could be targeted directly or downstream through involvement of the mammalian Target of Rapamycin (mTOR) pathway [100, 101].

Several studies thus far have documented antitumor activity associated with TK inhibitor, anti-VEGF monoclonal antibody as well as mTOR inhibitors in patients with NETs. These studies have led to the approval of some of these agents in the United States for treatment of advanced pan-

creatic NETs. However, the benefit of targeted therapy for gastrointestinal NETs is less well-established.

mTOR Inhibitors

Everolimus is an mTOR inhibitor whose antitumor effect was described in an international multicenter phase II trial, where patients were stratified by prior octreotide therapy to receive everolimus; or everolimus plus octreotide long-acting release after failure of cytotoxic chemotherapy in patients with metastatic pancreatic neuroendocrine tumors (RADIANT-1) [102]. The study results showed a PFS of 17 months in the combination arm versus 9.7 months in the everolimus alone arm, demonstrating the antitumor activity of mTOR inhibitor after failure of cytotoxic chemotherapy. But given that the study was not randomized, the contribution of octreotide to the higher PFS was unclear.

Unlike the response with metastatic pancreatic neuroendocrine tumors, metastatic gastrointestinal NETs did not show a significant response in a phase II study of 30 patients. Partial responses were observed in 17% of patients, but the median time to tumor progression was under 8 months [103]. Nevertheless, this prompted the RADIANT 2 trial, a phase III trial comparing long-acting octreotide with or without everolimus in 429 patients [104]. The study showed potentially clinically meaningful prolongation in median PFS, but a borderline statistical significance (16.4 versus 11.3 months; hazard ratio [HR] for tumor progression 0.77, 95% CI, 0.59–1.0). Furthermore, there was no significant difference in overall survival. But, after adjusting for randomization imbalances in the study, a significant PFS benefit was noted in the everolimus arm (HR for progression 0.62, 95% CI, 0.51–0.87, $P = 0.003$) [105].

The follow-up study in advanced progressing pancreatic NETs was the RADIANT-3 trial, which was a placebo-controlled trial that compared everolimus monotherapy to the best supportive care in 410 patients. It demonstrated a significant prolongation in median PFS in advanced progressing pancreatic NETs (11.0 versus 4.6 months, hazard ratio [HR] for progression 0.35, 95% CI, 0.27–0.45) [106]. Based upon these data, everolimus was approved in the United States for the treatment of pancreatic NETs in patients with unresectable local, advanced, or metastatic disease.

While the data on the effectiveness of everolimus is evident in advanced pancreatic NETs, its role in advanced gastrointestinal NETs is not clear. A phase III study, RADIANT-4, is comparing everolimus to placebo in advanced, nonfunctional lung or gastrointestinal NETs. The study has completed accrual and is waiting on final results, which will provide additional information regarding the activity of everolimus in the treatment of non-pancreatic NET.

Everolimus is associated with significant side effects including rash, fatigue, diarrhea, stomatitis, pneumonitis, hyperglycemia, thrombocytopenia, anemia, and infection.

Temsirolimus is another mTOR inhibitor, whose efficacy in pancreatic NET was evaluated in a phase II study of 37 patients. The results did not show significant response, but 67% of the patients had disease control [107] (Table 16.5 [102, 104, 106–110]).

Vascular Endothelial Growth Factor

Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting VEGF-A. Its activity was initially demonstrated in a phase II trial of 44 patients with metastatic gastrointestinal NETs. Patients were randomized to bevacizumab versus pegylated

Table 16.5 Studies of NETs treated with mTOR inhibitors

Study	Type	Tumor	Regimen	*N*	RR (%)	PFS (mo)	OS (mo)
Duran et al. [107]	Non-randomized	PENT carcinoid	Tem	15 21	7 5	10.6 6	NR
Yao et al. [102] (RADIANT-1)	Non-randomized	PENT	Eve Eve + Octr	115 45	9 4	9.7 16.7	NR
Yao et al. [106] (RADIANT-3)	Randomized	PENT	Eve Placebo	207 203	5 2	11[a] 4.6	44 37.7
Pavel et al. [104] (RADIANT-2)	Randomized	Carcinoid	Eve + Octr Octr	216 213	2 2	16.4[a] 11.3	NR
Yao et al. [108] (RADIANT-4)	Randomized	Carcinoid	Eve Placebo	304	2 1	11[a] 3.9	
Kulke et al. [109] (CALGB 80701)	Randomized	PENT	Eve + BEV Eve	75 75	31[a] 12	17.7 14	36.7 35
NCT02246127 (SEQTOR) [110]	Randomized	PENT	STZ + 5-FU > Eve Eve > STZ + 5-FU	180			

Bev bevacizumab, *Cape* capecitabine, *Eve* everolimus, *5-FU* 5-Fluorouracil, *mo* Month, *NR* not reported, *PENT* pancreatic neuroendocrine tumor, *PFS* progression-free survival, *RR* response rate, *Octr* octreotide, *OS* overall survival, *STZ* streptozotocin, *Tem* temsirolimus
[a]Statistical significant difference

INFa-2b, but eventually patients would receive both treatments if they progressed or reached 18 weeks of treatment [99]. The results showed that 77% of patients treated with bevacizumab had stable disease, and after 18 weeks, 95% of patients treated with the combination remained progression-free. These results led to a phase III trial comparing octreotide plus bevacizumab to octreotide plus interferon in unresectable or metastatic gastrointestinal or lung NETs. The preliminary report presented at the 2015 annual American Society of Clinical Oncology (ASCO) meeting showed that radiologic responses were more frequent among patients treated with bevacizumab, but median PFS was not significantly different [111].

In metastatic pancreatic NETs, the combination of bevacizumab and everolimus is being evaluated in a phase II trial [109]. Preliminary results presented at the 2015 ASCO meeting demonstrated significantly higher response rates and PFS in the combination arm versus everolimus alone, but no overall survival benefit was reported (Table 16.6) [99, 109, 111–113].

Tyrosine Kinase Inhibitors

The activity of TK inhibitor, similar to mTOR inhibitor, has been better demonstrated with pancreatic NETs. Sunitinib is a multitargeted TK inhibitor with the most experience. Its activity in pancreatic NETs was initially demonstrated in a phase II trial of 109 patients who showed an 18% partial response and 68% stable disease [114]. A phase III placebo control trial of 171 patients with pancreatic NETs was stopped prematurely prior to the first preplanned interim efficacy analysis [115]. The median PFS was significantly longer with sunitinib: 11.4 versus 5.5 months in the control arm. Based upon this, sunitinib was approved in the United States.

The other TK inhibitors include sorafenib, a VEGFR-2 and PDGFR-beta inhibitor, and pazopanib, which targets EGFR-1, VEGFR-2, VEGFR-3, PDGFR-alpha and beta, as well as KIT. The latter was evaluated in a phase II single-agent study of 51 patients with advanced NET who received pazopanib plus long-acting octreotide. The results showed a response rate of 22% in patients with pancreatic NETs, but not for gastrointestinal tumors [116]. Nevertheless, a randomized phase II trial is being conducted by the Alliance for Clinical Trials in Oncology Group (ACOG) evaluating the efficacy of pazopanib compared with placebo for patients with advanced carcinoid tumors (NCT01841736). Sorafenib's antitumor effect was evaluated in 43 patients with pancreatic NETs. Preliminary analysis showed a 9% response [117] (Table 16.7 [114–116, 118–120]).

Table 16.6 Studies of NETs treated with bevacizumab

Study	Type	Tumor	Regimen	*N*	RR (%)	PFS (mo)	OS (mo)
Yao et al. [99]	Randomized	Carcinoid	Bev + Octr PEG INF + Octr	44	18 0	16.5 14	NR
Hobday et al. [112]	Non-randomized	PENT	Bev	22	9	13.6	NR
Yao et al. [111] (SWOG S0518)	Randomized	Carcinoid	Bev + Octr PEG INF + Octr	423	12 4	16.6 14.5	NR
Hobday et al. [112]	Non-randomized	PENT	Bev + Tem	58	41	13.2	34
Kulke et al. [109] (9CALGB 80701)	Randomized	PENT	Eve + BEV Eve	75 75	31[a] 12	17.7 14	36.7 35
NCT01525082 [113]	Non-randomized	PENT	Bev + Cape + Tem	180			

Bev bevacizumab, *Cape* capecitabine, *mo* Month, *NR* not reported, *PENT* pancreatic neuroendocrine tumor, *PEG INF* Pegylated interferon Alpha-2b, *PFS* progression-free survival, *RR* response rate, *Octr* octreotide, *OS* overall survival, *Tem* temsirolimus
[a]Statistical significant difference

Table 16.7 Studies of NETs treated with tyrosine kinase inhibitors

Study	Type	Tumor	Regimen	*N*	RR (%)	PFS (mo)	OS (mo)
Hobday et al. [118]	Non-randomized	PENT carcinoid	Sorafenib	43 50	10 10	NR	NR
Kulke et al. [114]	Non-randomized	PENT carcinoid	Sunitinib	66 41	17 2	7.7 10.2	NR
Raymond et al. [115]	Randomized	PENT	Sunitinib Placebo	171	9 0	11.4[a] 5.5	NR
Phan et al. [116]	Non-randomized	PENT carcinoid	Pazopanib + Octr	32 20	22 0	14.4 12.2	25 18.5
NCT01465659 [119]	Non- randomized	PENT	Pazopanib + TMZ	39			
NCT01841736 [120]	Randomized	Carcinoid	Pazopanib Placebo	165			

mo month, *NR* not reported, *PENT* pancreatic neuroendocrine tumor, *PFS* progression-free survival, *RR* response rate, *Octr* octreotide, *OS* overall survival, *TMZ* temozolomide
[a]Statistical significant difference

Cytotoxic Chemotherapy

The benefit of cytotoxic chemotherapies in pancreatic NETs is well documented, and its use is encouraged in symptomatic patients with increasing tumor bulk or rapid progression. However, in gastrointestinal NETs, the benefit is less clear with rare objective radiologic responses and a lack of a substantial progression-free survival or overall survival benefit in clinical trials. Therefore, the NANETS, ENETS, and NCCN guidelines indicate that chemotherapy may be considered in patients with progressive disease for whom no other treatment options are available.

Streptozocin

Historically, streptozocin-based combination therapy has been the standard treatment for patients with advanced pancreatic NETs, and it is the most studied in gastrointestinal NETs. Various trials evaluating streptozocin combination with fluorouracil, bevacizumab, or cyclophosphamide in gastrointestinal NETs did not show substantial radiographic response rate nor statistically significant median survival benefit (Table 16.8) [121–129]. However, in pancreatic NETs, the antitumor effects have been well established in an early randomized trial of streptozocin plus doxorubicin and subsequent retrospective analyses of streptozocin plus doxorubicin and/or fluorouracil [125, 130, 131]. But, given streptozocin cumbersome administration schedule and significant toxicity, its use has been limited.

Dacarbazine is an alkylating agent that is similar to streptozocin with its activity against pancreatic NET but also with its associated toxicity. In an ECOG phase II trial of 42 patients with advanced pancreatic NETs, dacarbazine was shown to have an objective response rate of 33% [132]. In a Southwest Oncology Group (SWOG) phase II trial in gastrointestinal NETs, patients received dacarbazine; the overall tumor response rate was 16% [133]. Nausea and/or vomiting were reported in 88% of patients.

Temozolomide is an oral analog of dacarbazine that is better tolerated. In a retrospective series of patients with NETs, temozolomide's single-agent activity was demonstrated in pancreatic NETs with a reported objective tumor response of 34%. However, only 2% of patients with gastrointestinal NETs had an objective tumor response [126]. Similarly, the combinations of temozolomide with thalidomide, bevacizumab, or everolimus in pancreatic NETs have also been shown to improve overall response rates [134–136]. Furthermore, temozolomide in combination with capecitabine has shown promise in a retrospective study of 30 patients with metastatic pancreatic NETs with a 70% response rate [127]. An ongoing phase II trial by ECOG is currently recruiting to evaluate temozolomide plus capecitabine versus temozolomide alone (NCT01824875).

The data for oxaliplatin-containing regimens in advanced gastrointestinal and in pancreatic NETs have been limited. Primary reporting from a phase II trial has hinted of the antitumor effects of capecitabine in combination with oxaliplatin and bevacizumab. Preliminary reports have indicated partial response and stable disease [137]. Furthermore, the combination of capecitabine and bevacizumab was evaluated in a phase II tail of 49 patients with metastatic gastrointestinal NETs. The study showed 18% partial response and 70% stable disease, but 84% of patient experienced grade 3 or 4 treatment-related toxicity [138].

Table 16.8 Studies of NETs treated with chemotherapy

Study	Type	Tumor	Regimen	*N*	RR (%)	PFS (mo)	OS (mo)
Moertel and Hanley [121]	Randomized	Carcinoid	5-FU + STZ CTX + STZ	118	33 26	NR NR	NR NR
Moertel et al. [124]	Randomized	PENT	5-FU + STZ STZ	84	63 36	NR NR	26 16.5
Moertel et al. [125]	Randomized	PNET	DOX + STZ 5-FU + STZ	105	69[a] 45	20[a] 6.9	26.4[a] 16.8
Sun et al. [123]	Randomized	Carcinoid	5-FU + STZ 5-FU + DOX	176	16 15.9	5.3 4.5	24.3[a] 15.7
Kulke et al. [126]	Retrospective	PENT	TMZ combinations	53	34	13.6	35.3
Strosberg et al. [127]	Non-randomized	PENT	TMZ + Cape	30	70	18	NR
Meyer et al. [128]	Randomized	PENT/others	STZ + Cape + Cisp STZ + Cape	86	16 12	9.7 10.2	27.5 26.7
NCT01824875 (ECOG 2211) [129]	Randomized	PENT	TMZ + Cape TMZ	145			

Cape capecitabine, *Cisp* Cisplatin, *CTX* cyclophosphamide, *DOX* doxorubicin, *5-FU* 5-Fluorouracil, *mo* Month, *NR* not reported, *PENT* pancreatic neuroendocrine tumor, *PFS* progression-free survival, *RR* response rate, *OS* overall survival, *STZ* streptozotocin, *TMZ* temozolomide
[a]Statistical significant difference

Poorly Differentiated Neuroendocrine Carcinomas

Toxic chemotherapy is the main treatment option for gastroenteropancreatic neuroendocrine carcinomas. Unfortunately, given the lack of data from prospective trials, treatment approaches are based primarily on retrospective reports and extrapolated recommendations for small cell lung cancer. Patients with poorly differentiated neuroendocrine carcinomas carry a poor prognosis given the rapid disease progression and high tendency for metastatic spread, even in patients with clinically localized tumors. As surgery alone is rarely curative, chemotherapy is the mainstay of treatment.

NANETS and ENETS guidelines, which are based on a small number of studies and inferred data for small cell cancer, recommend platinum-based regimen, generally cisplatin or carboplatin plus etoposide for 4–6 cycles, for initial systemic therapy [25, 139, 140]. Alternatively, irinotecan plus cisplatin combination may be used [141]. A platinum plus etoposide regimen may be considered as definitive or neoadjuvant, depending on whether surgical resection is feasible. However, distant recurrences are far more frequent than local recurrences, and almost all patients relapse and die of their disease.

The benefit of platinum (cisplatin) plus etoposide was initially noted in a study of 45 patients with metastatic NETs, of which 18 patients were classified as having neuroendocrine carcinomas. The patients were treated with etoposide 130 mg/m^2 per day on days 1–3 and cisplatin 45 mg/m^2 per day on days 2 and 3. Out of the 18 patients with neuroendocrine carcinomas, 12 (67%) experienced objective response and 3 complete regression. The median duration of regression was 8 months [139]. In another retrospective analysis of 41 patients with gastroenteropancreatic neuroendocrine carcinomas treated with etoposide 100 mg/m^2 per day on days 1 through 3 and cisplatin 100 mg/m^2 on day 1 every 21 days, 42% of patients had an objective response and 4 complete responses. The median duration of response was 9.2 months, with a median survival of 15 months [140].

The efficacy of cisplatin versus carboplatin plus etoposide was assessed in a large Nordic consortium retrospective study of 252 patients with gastroenteropancreatic neuroendocrine carcinomas. The data did not show significant differences in outcomes whether patients were treated with cisplatin or carboplatin. The response rate was 31%, progression-free survival was 4 months, and median survival was 11 months. Interestingly, Ki-67 higher than 55% was predictive for response to chemotherapy, as tumors with Ki-67 below 55% were less responsive to platinum-based chemotherapy, with a response rate of 15% versus 42% in high Ki-67 tumors. Furthermore, median overall survival was significantly longer in high Ki-67 tumors (14 versus 10 months) [142].

Irinotecan as a substitute for etoposide was validated as an alternative first-line regimen in small cell lung cancer, and preliminary experience in gastroenteropancreatic neuroendocrine carcinomas has been promising [141, 143]. However, there are no trials directly comparing both regimens as of now; a phase III study is currently ongoing in Japan.

The addition of paclitaxel to platinum plus etoposide was evaluated in a single-arm phase II trial of 78 patients in metastatic poorly differentiated neuroendocrine carcinoma. The results showed an overall response rate of 53%, and median survival was 14.5 months, but grade 3 and 4 toxicities were frequent [144]. However, given that the 3-drug regimen was not directly compared to platinum-based doublet, it is unclear if these results represent improvement.

The data in second-line therapy is very limited with no established standard regimen. Patients who progress more than 3 months after completion of first-line treatment may still respond to platinum regimen as described in the Nordic neuroendocrine carcinoma study. Patients retreated with the platinum doublet had a response rate of 15% and 27% stable disease [142].

Other systemic treatments include oxaliplatin, irinotecan, topotecan, and temozolomide-based chemotherapy. A study evaluating 17 patients treated with oxaliplatin, fluorouracil plus leucovorin (FOLFOX) after progression on platinum-based regimen reported 29% of patients had partial response and 33% stable disease [145]. Irinotecan, fluorouracil plus leucovorin (FOLFIRI) efficacy was assessed in a study of 19 patients with platinum-resistant neuroendocrine carcinoma. The response rate was 31%, and median PFS was 4 months [146]. Recently, a 2-case study evaluating the effectiveness of oxaliplatin, irinotecan, fluorouracil plus leucovorin (modified FOLFIRINOX) reported promising results [147].

The activity of topotecan is well established in small cell lung cancer, but in a small retrospective analysis of 22 patients with gastroenteropancreatic neuroendocrine carcinomas, 77% of patients had immediate disease progression, 23% had stable disease, and median survival was only 3.2 months [148].

Finally, temozolomide-based treatment, which is used in the second-line setting, has not been convincing. A study evaluating 25 patients with gastroenteropancreatic neuroendocrine carcinomas who received temozolomide with or without capecitabine and bevacizumab reported a 33% response rate, 38% stable disease, and 22 months median overall survival [149]. However, in a study of 28 patients treated with temozolomide monotherapy, there were no responses, and median survival was only 3.5 months [150]. Patients with Ki-67 below 50% did better with median survival of 10.9 versus 2.7 months in patients with high Ki-67 (>50%).

As noted earlier, several studies have challenged the assumption that poorly differentiated histology and high tumor grade are equivalent [5, 151]. It seems that a small subset of patients with neuroendocrine tumors that appear histologically well or moderately differentiated are associated with Ki-67 proliferation indices higher than 20%, usually in the 20–55% range [152]. Multiple studies have showed low response rates to platinum plus etoposide regimens in this subset, and the appropriate systemic therapy remains unclear [142, 152]. Possible treatment may include somatostatin analogs, molecularly targeted such as mTOR, and VEGF inhibitors, temozolomide or chemotherapy. More studies are required.

References

1. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Diaz-Perez JA, Martinez Del Prado MP, Alonso Orduna V, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the national cancer registry of spain (RGETNE). Ann Oncol. [Research Support, Non-U.S. Gov't Review]. 2010;21(9):1794–803.
2. Mocellin S, Nitti D. Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n = 25 531). Ann Oncol. 2013;24(12):3040–4.
3. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934–59.
4. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72.
5. Vélayoudom-Céphise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer. 2013;20(5):649–57.
6. Zárate X, Williams N, Herrera MF. Pancreatic incidentalomas. Best Pract Res Clin Endocrinol Metab. 2012;26(1):97–103.
7. Korse CM, Taal BG, van Velthuysen ML, Visser O. Incidence and survival of neuroendocrine tumours in the netherlands according to histological grade: experience of two decades of cancer registry. Eur J Cancer. 2013;49(8):1975–83.
8. Berge T, Linell F. Carcinoid tumours. Frequency in a defined population during a 12-year period. Acta Pathol Microbiol Scand A. 1976;84(4):322–30.
9. Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from sweden. Cancer. 2001;92(8):2204–10.
10. Kang H, O'Connell JB, Leonardi MJ, Maggard MA, McGory ML, Ko CY. Rare tumors of the colon and rectum: a national review. Int J Colorectal Dis. 2007;22(2):183–9.
11. Dasari A, Mehta K, Byers LA, Sorbye H, Yao JC. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: a seer database analysis of 162,983 cases. Cancer. 2018;124(4):807–15.
12. Tsai HJ, Wu CC, Tsai CR, Lin SF, Chen LT, Chang JS. The epidemiology of neuroendocrine tumors in taiwan: a nation-wide cancer registry-based study. PLoS One. 2013;8(4):e62487.
13. Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijen ML, Taal BG. Epidemiology and survival in patients with carcinoid disease in the netherlands. An epidemiological study with 2391 patients. Ann Oncol. 2001;12(9):1295–300.
14. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121(4):589–97.
15. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. Ann Surg. 2004;240(1):117–22.
16. Taghavi S, Jayarajan SN, Powers BD, Davey A, Willis AI. Examining rectal carcinoids in the era of screening colonoscopy: a surveillance, epidemiology, and end results analysis. Dis Colon Rectum. 2013;56(8):952–9.
17. Tsoucalas G, Karamanou M, Androutsos G. The eminent german pathologist siegfried oberndorfer (1876–1944) and his landmark work on carcinoid tumors. Ann Gastroenterol. 2011;24(2):98–100.
18. Dakin GF, Warner RR, Pomp A, Salky B, Inabnet WB. Presentation, treatment, and outcome of type 1 gastric carcinoid tumors. J Surg Oncol. 2006;93(5):368–72.
19. Capella C, Heitz PU, Höfler H, Solcia E, Klöppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. Virchows Arch. 1995;425(6):547–60.
20. Saha S, Hoda S, Godfrey R, Sutherland C, Raybon K. Carcinoid tumors of the gastrointestinal tract: a 44-year experience. South Med J. 1989;82(12):1501–5.
21. Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. J Surg Oncol. 2005;89(3):151–60.
22. Spread C, Berkel H, Jewell L, Jenkins H, Yakimets W. Colon carcinoid tumors. A population-based study. Dis Colon Rectum. 1994;37(5):482–91.
23. Shields CJ, Tiret E, Winter DC, Group IRCS. Carcinoid tumors of the rectum: a multi-institutional international collaboration. Ann Surg. 2010;252(5):750–5.
24. Walenkamp AM, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. Cancer Treat Rev. 2009;35(3):228–36.
25. Janson ET, Sorbye H, Welin S, Federspiel B, Grønbæk H, Hellman P, et al. Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. Acta Oncol. 2014;53(10):1284–97.
26. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39(6):707–12.
27. Tang LH, Basturk O, Sue JJ, Klimstra DS. A practical approach to the classification of who grade 3 (G3) well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC) of the pancreas. Am J Surg Pathol. 2016;40(9):1192–202.
28. Gustafsson BI, Kidd M, Chan A, Malfertheiner MV, Modlin IM. Bronchopulmonary neuroendocrine tumors. Cancer. 2008;113(1):5–21.
29. La Rosa S, Sessa F. High-grade poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic system: from morphology to proliferation and back. Endocr Pathol. 2014;25(2):193–8.
30. Hochwald SN, Zee S, Conlon KC, Colleoni R, Louie O, Brennan MF, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. J Clin Oncol. 2002;20(11):2633–42.
31. Travis WD, Rush W, Flieder DB, Falk R, Fleming MV, Gal AA, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol. 1998;22(8):934–44.
32. Shia J, Tang LH, Weiser MR, Brenner B, Adsay NV, Stelow EB, et al. Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? Am J Surg Pathol. 2008;32(5):719–31.

33. Yang Z, Tang LH, Klimstra DS. Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. Am J Surg Pathol. 2011;35(6):853–60.
34. Jann H, Roll S, Couvelard A, Hentic O, Pavel M, Müller-Nordhorn J, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. Cancer. 2011;117(15):3332–41.
35. Dolcetta-Capuzzo A, Villa V, Albarello L, Franchi GM, Gemma M, Scavini M, et al. Gastroenteric neuroendocrine neoplasms classification: comparison of prognostic models. Cancer. 2013;119(1):36–44.
36. Strosberg JR, Weber JM, Feldman M, Coppola D, Meredith K, Kvols LK. Prognostic validity of the American Joint Committee on cancer staging classification for midgut neuroendocrine tumors. J Clin Oncol. 2013;31(4):420–5.
37. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology. 2005;128(6):1717–51.
38. Kvols LK. Metastatic carcinoid tumors and the malignant carcinoid syndrome. Ann N Y Acad Sci. 1994;733:464–70.
39. Oates JA. The carcinoid syndrome. N Engl J Med. 1986;315(11):702–4.
40. Cunningham JL, Janson ET, Agarwal S, Grimelius L, Stridsberg M. Tachykinins in endocrine tumors and the carcinoid syndrome. Eur J Endocrinol. 2008;159(3):275–82.
41. Maton PN. The carcinoid syndrome. JAMA. 1988; 260(11):1602–5.
42. von der Ohe MR, Camilleri M, Kvols LK, Thomforde GM. Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. N Engl J Med. 1993;329(15):1073–8.
43. Swain CP, Tavill AS, Neale G. Studies of tryptophan and albumin metabolism in a patient with carcinoid syndrome, pellagra, and hypoproteinemia. Gastroenterology. 1976;71(3):484–9.
44. Bivens CH, Marecek RL, Feldman JM. Peyronie's disease--a presenting complaint of the carcinoid syndrome. N Engl J Med. 1973;289(16):844–5.
45. Woodside KJ, Townsend CM, Evers BM. Current management of gastrointestinal carcinoid tumors. J Gastrointest Surg. 2004;8(6):742–56.
46. Davì MV, Bodei L, Francia G, Bartolomei M, Oliani C, Scilanga L, et al. Carcinoid crisis induced by receptor radionuclide therapy with 90Y-DOTATOC in a case of liver metastases from bronchial neuroendocrine tumor (atypical carcinoid). J Endocrinol Invest. 2006;29(6):563–7.
47. Lewis MA, Jaramillo S, Roberts L, Fleming CJ, Rubin J, Grothey A. Hepatic artery embolization for neuroendocrine tumors: postprocedural management and complications. Oncologist. 2012;17(5):725–31.
48. Sjöblom SM. Clinical presentation and prognosis of gastrointestinal carcinoid tumours. Scand J Gastroenterol. 1988;23(7):779–87.
49. Modlin IM, Gustafsson BI, Moss SF, Pavel M, Tsolakis AV, Kidd M. Chromogranin a--biological function and clinical utility in neuro endocrine tumor disease. Ann Surg Oncol. 2010;17(9):2427–43.
50. Campana D, Nori F, Piscitelli L, Morselli-Labate AM, Pezzilli R, Corinaldesi R, et al. Chromogranin A: is it a useful marker of neuroendocrine tumors? J Clin Oncol. 2007;25(15):1967–73.
51. Vezzosi D, Walter T, Laplanche A, Raoul JL, Dromain C, Ruszniewski P, et al. Chromogranin a measurement in metastatic well-differentiated gastroenteropancreatic neuroendocrine carcinoma: screening for false positives and a prospective follow-up study. Int J Biol Markers. 2011;26(2):94–101.
52. Pregun I, Herszényi L, Juhász M, Miheller P, Hritz I, Patócs A, et al. Effect of proton-pump inhibitor therapy on serum chromogranin a level. Digestion. 2011;84(1):22–8.
53. Shah T, Srirajaskanthan R, Bhogal M, Toubanakis C, Meyer T, Noonan A, et al. Alpha-fetoprotein and human chorionic gonadotrophin-beta as prognostic markers in neuroendocrine tumour patients. Br J Cancer. 2008;99(1):72–7.
54. Ganeshan D, Bhosale P, Yang T, Kundra V. Imaging features of carcinoid tumors of the gastrointestinal tract. AJR Am J Roentgenol. 2013;201(4):773–86.
55. Dromain C, de Baere T, Lumbroso J, Caillet H, Laplanche A, Boige V, et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. J Clin Oncol. 2005;23(1):70–8.
56. Schirmer WJ, Melvin WS, Rush RM, O'Dorisio TM, Pozderac RV, Olsen JO, et al. Indium-111-pentetreotide scanning versus conventional imaging techniques for the localization of gastrinoma. Surgery. 1995;118(6):1105–13; discussion 1113–4.
57. Reidy-Lagunes DL, Gollub MJ, Saltz LB. Addition of octreotide functional imaging to cross-sectional computed tomography or magnetic resonance imaging for the detection of neuroendocrine tumors: added value or an anachronism? J Clin Oncol. 2011;29(3):e74–5.
58. Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas. 2013;42(4):557–77.
59. Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, et al. Enets consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology. 2012;95(2):135–56.
60. Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, et al. Enets consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 2012;95(2):157–76.
61. Koopmans KP, Neels OC, Kema IP, Elsinga PH, Sluiter WJ, Vanghillewe K, et al. Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. J Clin Oncol. 2008;26(9):1489–95.
62. Buchmann I, Henze M, Engelbrecht S, Eisenhut M, Runz A, Schäfer M, et al. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2007;34(10):1617–26.
63. Toste PA, Kadera BE, Tatishchev SF, Dawson DW, Clerkin BM, Muthusamy R, et al. Nonfunctional pancreatic neuroendocrine tumors <2 cm on preoperative imaging are associated with a low incidence of nodal metastasis and an excellent overall survival. J Gastrointest Surg. 2013;17(12):2105–13.
64. Sadot E, Reidy-Lagunes DL, Tang LH, Do RK, Gonen M, D'Angelica MI, et al. Observation versus resection for small asymptomatic pancreatic neuroendocrine tumors: a matched case-control study. Ann Surg Oncol. [Comparative Study Observational Study Research Support, N.I.H., Extramural]. 2016;23(4):1361–70.
65. Sharpe SM, In H, Winchester DJ, Talamonti MS, Baker MS. Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. J Gastrointest Surg. 2015;19(1):117–23; discussion 123.
66. Poultsides GA, Huang LC, Chen Y, Visser BC, Pai RK, Jeffrey RB, et al. Pancreatic neuroendocrine tumors: radiographic calcifications correlate with grade and metastasis. Ann Surg Oncol. 2012;19(7):2295–303.
67. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Comparison of surgical results in patients with advanced and

limited disease with multiple endocrine neoplasia type 1 and zollinger-ellison syndrome. Ann Surg. [Comparative Study]. 2001;234(4):495–505; discussion 505–6
68. Gladdy RA, Strong VE, Coit D, Allen PJ, Gerdes H, Shia J, et al. Defining surgical indications for type I gastric carcinoid tumor. Ann Surg Oncol. 2009;16(11):3154–60.
69. Norton JA, Melcher ML, Gibril F, Jensen RT. Gastric carcinoid tumors in multiple endocrine neoplasia-1 patients with zollinger-ellison syndrome can be symptomatic, demonstrate aggressive growth, and require surgical treatment. Surgery. 2004;136(6):1267–74.
70. Trendle MC, Moertel CG, Kvols LK. Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. Cancer. 1997;79(4):830–4.
71. Sutton R, Doran HE, Williams EM, Vora J, Vinjamuri S, Evans J, et al. Surgery for midgut carcinoid. Endocr Relat Cancer. [Research Support, Non-U.S. Gov't Review]. 2003;10(4):469–81.
72. Ohrvall U, Eriksson B, Juhlin C, Karacagil S, Rastad J, Hellman P, et al. Method for dissection of mesenteric metastases in midgut carcinoid tumors. World J Surg. [Comparative Study Research Support, Non-U.S. Gov't]. 2000;24(11):1402–8.
73. Woltering EA, Wright AE, Stevens MA, Wang YZ, Boudreaux JP, Mamikunian G, et al. Development of effective prophylaxis against intraoperative carcinoid crisis. J Clin Anesth. 2016;32:189–93.
74. Luis SA, Pellikka PA. Carcinoid heart disease: diagnosis and management. Best Pract Res Clin Endocrinol Metab. [Review]. 2016;30(1):149–58.
75. Mayo SC, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Surg Oncol. [Multicenter Study]. 2010;17(12):3129–36.
76. Mayo SC, de Jong MC, Bloomston M, Pulitano C, Clary BM, Reddy SK, et al. Surgery versus intra-arterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. Ann Surg Oncol. [Multicenter Study]. 2011;18(13):3657–65.
77. Vilchez V, Gedaly R. Liver transplantation for the treatment of neuroendocrine liver metastases. Best Pract Res Clin Endocrinol Metab. [Review]. 2016;30(1):141–7.
78. Mazzaferro V, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. Am J Transplant. 2016;16(10):2892–902.
79. Duerr EM, Chung DC. Molecular genetics of neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab. 2007;21(1):1–14.
80. Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer. 2005;12(4):1083–92.
81. Bousquet C, Lasfargues C, Chalabi M, Billah SM, Susini C, Vezzosi D, et al. Clinical review: current scientific rationale for the use of somatostatin analogs and mtor inhibitors in neuroendocrine tumor therapy. J Clin Endocrinol Metab. 2012;97(3):727–37.
82. Janson ET, Westlin JE, Eriksson B, Ahlström H, Nilsson S, Oberg K. [111In-DTPA-D-Phe1]octreotide scintigraphy in patients with carcinoid tumours: the predictive value for somatostatin analogue treatment. Eur J Endocrinol. 1994;131(6):577–81.
83. Anthony L, Vinik AI. Evaluating the characteristics and the management of patients with neuroendocrine tumors receiving octreotide lar during a 6-year period. Pancreas. 2011;40(7):987–94.
84. Toumpanakis C, Garland J, Marelli L, Srirajaskanthan R, Soh J, Davies P, et al. Long-term results of patients with malignant carcinoid syndrome receiving octreotide lar. Aliment Pharmacol Ther. 2009;30(7):733–40.
85. Eriksson B, Renstrup J, Imam H, Oberg K. High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. Ann Oncol. 1997;8(10):1041–4.
86. Tomassetti P, Migliori M, Gullo L. Slow-release lanreotide treatment in endocrine gastrointestinal tumors. Am J Gastroenterol. 1998;93(9):1468–71.
87. di Bartolomeo M, Bajetta E, Buzzoni R, Mariani L, Carnaghi C, Somma L, et al. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the italian trials in medical oncology group. Cancer. 1996;77(2):402–8.
88. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide lar in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the promid study group. J Clin Oncol. 2009;27(28):4656–63.
89. Sidéris L, Dubé P, Rinke A. Antitumor effects of somatostatin analogs in neuroendocrine tumors. Oncologist. 2012;17(6):747–55.
90. Faiss S, Pape UF, Böhmig M, Dörffel Y, Mansmann U, Golder W, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the international lanreotide and interferon alfa study group. J Clin Oncol. 2003;21(14):2689–96.
91. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–33.
92. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (nets). Gut. 2012;61(1):6–32.
93. Broder MS, Beenhouwer D, Strosberg JR, Neary MP, Cherepanov D. Gastrointestinal neuroendocrine tumors treated with high dose octreotide-lar: a systematic literature review. World J Gastroenterol. 2015;21(6):1945–55.
94. Woltering EA, Mamikunian PM, Zietz S, Krutzik SR, Go VL, Vinik AI, et al. Effect of octreotide lar dose and weight on octreotide blood levels in patients with neuroendocrine tumors. Pancreas. 2005;31(4):392–400.
95. O'Toole D, Ducreux M, Bommelaer G, Wemeau JL, Bouché O, Catus F, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. Cancer. 2000;88(4):770–6.
96. Bajetta E, Zilembo N, Di Bartolomeo M, Di Leo A, Pilotti S, Bochicchio AM, et al. Treatment of metastatic carcinoids and other neuroendocrine tumors with recombinant interferon-alpha-2a. A study by the italian trials in medical oncology group. Cancer. 1993;72(10):3099–105.
97. Dirix LY, Vermeulen PB, Fierens H, De Schepper B, Corthouts B, Van Oosterom AT. Long-term results of continuous treatment with recombinant interferon-alpha in patients with metastatic carcinoid tumors--an antiangiogenic effect? Anticancer Drugs. 1996;7(2):175–81.
98. Moertel CG, Rubin J, Kvols LK. Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte a interferon. J Clin Oncol. 1989;7(7):865–8.
99. Yao JC, Phan A, Hoff PM, Chen HX, Charnsangavej C, Yeung SC, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. J Clin Oncol. 2008;26(8):1316–23.
100. Oberg K, Casanovas O, Castaño JP, Chung D, Delle Fave G, Denèfle P, et al. Molecular pathogenesis of neuroendocrine tumors: implications for current and future therapeutic approaches. Clin Cancer Res. 2013;19(11):2842–9.

101. Zhang J, Francois R, Iyer R, Seshadri M, Zajac-Kaye M, Hochwald SN. Current understanding of the molecular biology of pancreatic neuroendocrine tumors. J Natl Cancer Inst. 2013;105(14):1005–17.
102. Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol. 2010;28(1):69–76.
103. Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol. 2008;26(26):4311–8.
104. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (radiant-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378(9808):2005–12.
105. Yao JC, Hainsworth JD, Wolin EM, Pavel ME, Baudin E, Gross D, Ruszniewski P, Tomassetti P, Panneerselvam A, Saletan S, Klimovsky J. Multivariate analysis including biomarkers in the phase iii radiant-2 study of octreotide lar plus everolimus (e+o) or placebo (p+o) among patients with advanced neuroendocrine tumors (net). J Clin Oncol. 2012;30(15_suppl):4014.
106. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514–23.
107. Duran I, Kortmansky J, Singh D, Hirte H, Kocha W, Goss G, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. Br J Cancer. [Clinical Trial, Phase II Research Support, N.I.H., Extramural]. 2006;95(9):1148–54.
108. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (radiant-4): a randomised, placebo-controlled, phase 3 study. Lancet. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2016;387(10022):968–77.
109. Kulke MH, Niedzwiecki D, Foster NR, Fruth B, Kunz PL, Kennecke HF, Wolin EM, Venook AP. Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (alliance). 2015.
110. Anonymous. Nct02246127. ClinicalTrials.gov.
111. Yao JC, Guthrie K, Moran C, Strosberg JR, Kulke MH, Chan JA, et al. Swog s0518: phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis carcinoid patients (NCT00569127). 2015.
112. Hobday TJ, Qin R, Reidy-Lagunes D, Moore MJ, Strosberg J, Kaubisch A, et al. Multicenter phase II trial of temsirolimus and bevacizumab in pancreatic neuroendocrine tumors. J Clin Oncol. [Clinical Trial, Phase II Multicenter Study Research Support, N.I.H., Extramural]. 2015;33(14):1551–6.
113. Anonymous. Nct01525082. ClinicalTrials.gov.
114. Kulke MH, Lenz HJ, Meropol NJ, Posey J, Ryan DP, Picus J, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol. 2008;26(20):3403–10.
115. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501–13.
116. Phan AT, Halperin DM, Chan JA, Fogelman DR, Hess KR, Malinowski P, et al. Pazopanib and depot octreotide in advanced, well-differentiated neuroendocrine tumours: a multicentre, single-group, phase 2 study. Lancet Oncol. 2015;16(6):695–703.
117. Raymond E, Hobday T, Castellano D, Reidy-Lagunes D, García-Carbonero R, Carrato A. Therapy innovations: tyrosine kinase inhibitors for the treatment of pancreatic neuroendocrine tumors. Cancer Metastasis Rev. 2011;30(Suppl 1):19–26.
118. Hobday TJ, Rubin J, Holen K, Picus J, Donehower R, Marschke R, Maples W, Lloyd R, Mahoney M, Erlichman C. Mc044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): a phase II consortium (P2C) study. J Clin Oncol. 2007;25(18 suppl):4504.
119. Anonymous. Nct01465659. ClinicalTrials.gov.
120. Anonymous. Nct01841736. ClinicalTrials.gov.
121. Moertel CG, Hanley JA. Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Clin Trials. 1979;2(4):327–34.
122. Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass HO. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol. 1984;2(11):1255–9.
123. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG, Eastern Cooperative Oncology Group. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: eastern cooperative oncology group study E1281. J Clin Oncol. 2005;23(22):4897–904.
124. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S.]. 1980;303(21):1189–94.
125. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med. 1992;326(8):519–23.
126. Kulke MH, Hornick JL, Frauenhoffer C, Hooshmand S, Ryan DP, Enzinger PC, et al. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. Clin Cancer Res. 2009;15(1):338–45.
127. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117(2):268–75.
128. Meyer T, Qian W, Caplin ME, Armstrong G, Lao-Sirieix SH, Hardy R, et al. Capecitabine and streptozocin ± cisplatin in advanced gastroenteropancreatic neuroendocrine tumours. Eur J Cancer. [Randomized Controlled Trial Research Support, Non--U.S. Gov't]. 2014;50(5):902–11.
129. Anonymous. Nct01824875. ClinicalTrials.gov.
130. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol. 2004;22(23):4762–71.
131. Dilz LM, Denecke T, Steffen IG, Prasad V, von Weikersthal LF, Pape UF, et al. Streptozocin/5-fluorouracil chemotherapy is associated with durable response in patients with advanced pancreatic neuroendocrine tumours. Eur J Cancer. 2015;51(10):1253–62.
132. Ramanathan RK, Cnaan A, Hahn RG, Carbone PP, Haller DG. Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the eastern cooperative oncology group-E6282. Ann Oncol. 2001;12(8):1139–43.
133. Bukowski RM, Tangen CM, Peterson RF, Taylor SA, Rinehart JJ, Eyre HJ, et al. Phase II trial of dimethyltriazenoimidazole carboxamide in patients with metastatic carcinoid. A southwest oncology group study. Cancer. 1994;73(5):1505–8.
134. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, et al. Phase II study of temozolomide and thalido-

mide in patients with metastatic neuroendocrine tumors. J Clin Oncol. 2006;24(3):401–6.
135. Chan JA, Stuart K, Earle CC, Clark JW, Bhargava P, Miksad R, et al. Prospective study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors. J Clin Oncol. 2012;30(24):2963–8.
136. Chan JA, Blaszkowsky L, Stuart K, Zhu AX, Allen J, Wadlow R, et al. A prospective, phase 1/2 study of everolimus and temozolomide in patients with advanced pancreatic neuroendocrine tumor. Cancer. 2013;119(17):3212–8.
137. Kunz PL, Kuo T, Zahn JM, Kaiser HL, Norton JA, Visser BC, Longacre TA, Ford JM, Balise RR, Fisher GA. A phase II study of capecitabine, oxaliplatin, and bevacizumab for metastatic or unresectable neuroendocrine tumors.
138. Mitry E, Walter T, Baudin E, Kurtz JE, Ruszniewski P, Dominguez-Tinajero S, et al. Bevacizumab plus capecitabine in patients with progressive advanced well-differentiated neuroendocrine tumors of the gastro-intestinal (GI-NETs) tract (BETTER trial)--a phase II non-randomised trial. Eur J Cancer. 2014;50(18):3107–15.
139. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer. 1991;68(2):227–32.
140. Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufié P, Aparicio T, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer. 1999;81(8):1351–5.
141. Yamaguchi T, Machida N, Morizane C, Kasuga A, Takahashi H, Sudo K, et al. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. Cancer Sci. 2014;105(9):1176–81.
142. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol. 2013;24(1):152–60.
143. Okita NT, Kato K, Takahari D, Hirashima Y, Nakajima TE, Matsubara J, et al. Neuroendocrine tumors of the stomach: chemotherapy with cisplatin plus irinotecan is effective for gastric poorly-differentiated neuroendocrine carcinoma. Gastric Cancer. 2011;14(2):161–5.
144. Hainsworth JD, Spigel DR, Litchy S, Greco FA. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a minnie pearl cancer research network study. J Clin Oncol. 2006;24(22):3548–54.
145. Hadoux J, Malka D, Planchard D, Scoazec JY, Caramella C, Guigay J, et al. Post-first-line folfox chemotherapy for grade 3 neuroendocrine carcinoma. Endocr Relat Cancer. 2015;22(3):289–98.
146. Hentic O, Hammel P, Couvelard A, Rebours V, Zappa M, Palazzo M, et al. Folfiri regimen: an effective second-line chemotherapy after failure of etoposide-platinum combination in patients with neuroendocrine carcinomas grade 3. Endocr Relat Cancer. 2012;19(6):751–7.
147. Zhu J, Strosberg JR, Dropkin E, Strickler JH. Treatment of high-grade metastatic pancreatic neuroendocrine carcinoma with folfirinox. J Gastrointest Cancer. 2015;46(2):166–9.
148. Olsen IH, Knigge U, Federspiel B, Hansen CP, Skov A, Kjær A, et al. Topotecan monotherapy in heavily pretreated patients with progressive advanced stage neuroendocrine carcinomas. J Cancer. 2014;5(8):628–32.
149. Welin S, Sorbye H, Sebjornsen S, Knappskog S, Busch C, Oberg K. Clinical effect of temozolomide-based chemotherapy in poorly differentiated endocrine carcinoma after progression on first-line chemotherapy. Cancer. 2011;117(20):4617–22.
150. Olsen IH, Sørensen JB, Federspiel B, Kjaer A, Hansen CP, Knigge U, et al. Temozolomide as second or third line treatment of patients with neuroendocrine carcinomas. Sci World J. 2012;2012:170496.
151. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer. 2014;120(18):2814–23.
152. Heetfeld M, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, et al. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer. 2015;22(4):657–64.

Gastrointestinal Stromal Tumors

17

Neeta Somaiah, Ridhi Gupta, and Shreyaskumar R. Patel

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract but as a group accounts for <1% of all GI tumors. They are thought to develop from connective tissue precursors in the GI tract—either the interstitial cells of Cajal or their pluripotent stem cell precursor. They rank a distant third in terms of prevalence among the different histologic subtypes of tumors of the GI tract after adenocarcinomas and lymphomas [1–3]. The diagnosis of GIST was underestimated prior to it being characterized molecularly, but recent experience from epidemiologic studies suggests that the annual incidence of GIST in the United States is at least 4000–6000 new cases (roughly 7–20 cases per million per year) [4–7].

GIST remains a classic example of the successful application of translational therapeutics in oncology, where the discovery of the molecular abnormalities characterizing GIST cells led to the use of a small-molecule inhibitor, imatinib, that revolutionized the treatment and outcomes for GIST patients [8, 9].

Presentation and Workup

GISTs arise as submucosal tumors in the GI tract that mostly grows parallel to the luminal structure but can also grow as exophytic masses. Primary GIST can grow anywhere along the GI tract but most commonly arise from the stomach (50–70%), followed by the small intestine—jejunoileum (35%), then the colon, rectum, anus (5–15%), and occasionally in the esophagus and other sites (<5%) [10–13]. Rarely, these tumors can arise from extra-intestinal sites, such as the omentum, gallbladder, urinary bladder, pancreas, prostate, and adrenal gland [14–18]. They can range in size from subcentimeter masses to as large as 40 cm. The clinical presentations vary depending on the site of origin, size of the tumor, and pattern of growth. Most common sites of metastasis occur in the liver and peritoneum but metastatic disease has been described in the lung, bones, brain, and subcutaneous tissues as well. Metastases to these rare sites have gone down significantly, to <5%, since the advent of imatinib [19, 20].

Clinical Features

Approximately, 70% of patients are symptomatic, 20% are asymptomatic, and 10% of cases are detected on autopsy [21]. Most symptomatic patients have tumors >5 cm in size and they usually present with either one or a combination of the following [22–24]:

- *Nonspecific symptoms* of fatigue, weakness, abdominal discomfort, early satiety.
- *Overt GI bleeding* and hemorrhage from the tumor.
- *Palpable mass and in some cases with mass effect*, which can cause site-specific symptoms of dysphagia (esophagus tumor), constipation, bowel obstruction, intussusception, or obstructive jaundice (duodenal). More serious presentations, such as bowel perforations, have also been reported and are associated with poorer prognosis.
- *Abdominal pain* is less common as a presenting symptom.
- *Paraneoplastic syndromes* can occur infrequently. Hypercalcemia can be seen in the metastatic setting likely from elevated calcitriol [25–27]. Hypothyroidism (proposed mechanism is an excessive degradation of thyroid hormone caused by overexpression of the thyroid hormone-inactivating enzyme type 3 iodothyronine deiodinase [D3])

N. Somaiah (✉) · S. R. Patel
Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: nsomaiah@mdanderson.org

R. Gupta (✉)
Department of Hematology and Medical Oncology, Maine General Medical Center/Harold Alfond Center for Cancer Care, Augusta, ME, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_17

and hypoglycemia (associated with high tumor burden and high levels of insulin-like growth factor II [IGF-II]) have also been reported [28, 29].

The peak incidence is in the fifth–sixth decades of life but there is a subset of GIST that arises in the pediatric population. The molecular makeup of tumors in this population tends to be different than adult-onset GIST and occasionally is associated with defined syndromes such as Carney triad seen in young women and Carney-Stratakis syndrome [21, 30, 31]. Per the Surveillance, Epidemiology, and End Results (SEER) database from 1992 to 2000, there is a slightly higher prevalence in males at 54% compared to females at 46% [32]. GISTs have no known racial preference. Based on a report by Cheung et al. of the 3795 patients diagnosed with mesenchymal tumors from the SEER database from 1992 to 2005, >88% of tumors were identified as GIST and the racial distribution included 72.2% Caucasians, 15.6% African Americans, and 9.1% Hispanics [33].

Diagnostic Workup

GIST may be suspected by finding of a subepithelial mass on endoscopy (EGD) or endoscopic ultrasound (EUS) or as an incidental finding on computed tomography (CT) scans or ultrasound that was performed for symptoms of abdominal pain, mass, or other symptoms. Contrast-enhanced CT scan (CECT) is the imaging of choice to help characterize an abdominal mass, organ of origin, extent of disease, and presence of metastatic disease. Magnetic resonance imaging (MRI) may also be used and has comparable yield as CECT, but is more expensive and time-consuming. MRI may be preferred for GISTs at specific sites such as the rectum and liver or in cases where iodinated contrast is contraindicated.

EUS is useful to further characterize a gastric mass identified on endoscopy, and tumors that disrupt the normal tissue planes, contain cystic spaces, and are noted to have lymphadenopathy are more likely to be malignant [34–36]. Endoscopic-guided fine needle aspiration (FNAC) or core biopsy is the preferred method for a biopsy as there is a theoretical risk of peritoneal seeding with a percutaneous biopsy secondary to the rupture of the tumor capsule. However, in the post-imatinib era, percutaneous biopsies do not appear to negatively impact outcome [37, 38]. If there is a high suspicion of GIST based on clinical and radiological features and the tumor is easily resectable, then a preoperative biopsy is not always required. If neoadjuvant imatinib to downsize the tumor would be beneficial, then obtaining a good quality pretreatment core biopsy is important to confirm the diagnosis, check for mutations, and provide information on the mitotic rate, which is important for risk assessment. In the case of metastatic disease, the most accessible metastasis should be biopsied.

Positron emission tomography (PET) scanning using fluoro-deoxyglucose (FDG) has a sensitivity of 86–100% for detecting GIST but is not specific for making a diagnosis. This high sensitivity makes it a good modality for initial staging to pick up metastases and for detecting response to imatinib. Early tumor response can be appreciated with a marked decrease in activity noted as early as 24 hours after treatment initiation [39]. Stroobants and colleagues in 2003 reported on PET scanning on 21 patients with soft tissue sarcomas (17 with GISTs) prior to beginning therapy and then 8 days after commencing therapy with imatinib. Responses were detected in 13 patients with GIST after just 8 days of therapy; and at 8 weeks, CT evidence of response was seen in 10 out of the 13 patients. This feature is helpful in management of GIST, especially in cases when response assessment with standard imaging is ambiguous (Fig. 17.1a–e) [40, 41].

Pathology and Pathogenesis

Initially, GISTs were thought to arise from stromal/mesenchymal elements based upon their histology. They can be classified into three histologic patterns: predominantly spindle cell (70%), epithelioid (20%), or both (10%) (Fig. 17.2a–d) [13]. The most critical breakthrough in our understanding of these tumors was the identification of the near universal expression of CD 117 (*KIT*) and the discovery of *KIT* (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue) proto-oncogene mutations that play a critical role in the pathogenesis of these tumors [42].

Histopathology

Immunohistochemical staining for *KIT* (CD117) can be detected in approximately 95% of GISTs and helps distinguish them from other GI tract sarcomas [5]. The 4–5% of GISTs that do not stain for KIT can pose a diagnostic challenge and mutation testing for *KIT* and *PDGFRA* should be performed if the tumor has a typical GIST morphology. In addition, DOG1 (discovered on GIST) immunohistochemical staining may be useful as it is a highly sensitive marker for GIST, and a subset of the *KIT*-negative GISTs expresses it [43]. It is important to remember that though *KIT* staining is considered diagnostic for GIST, there are a number of non-GISTs that can be positive for *KIT,* such as metastatic melanoma, angiosarcoma (50%), Ewing's sarcoma family of tumors (50%), childhood neuroblastoma (30%), extramedullary myeloid tumor, seminoma, and small-cell lung carcinoma. Thus, to make a diagnosis based on histologic evaluation, immunohistochemistry and molecular analysis are needed. Because of similarities in the staining patterns,

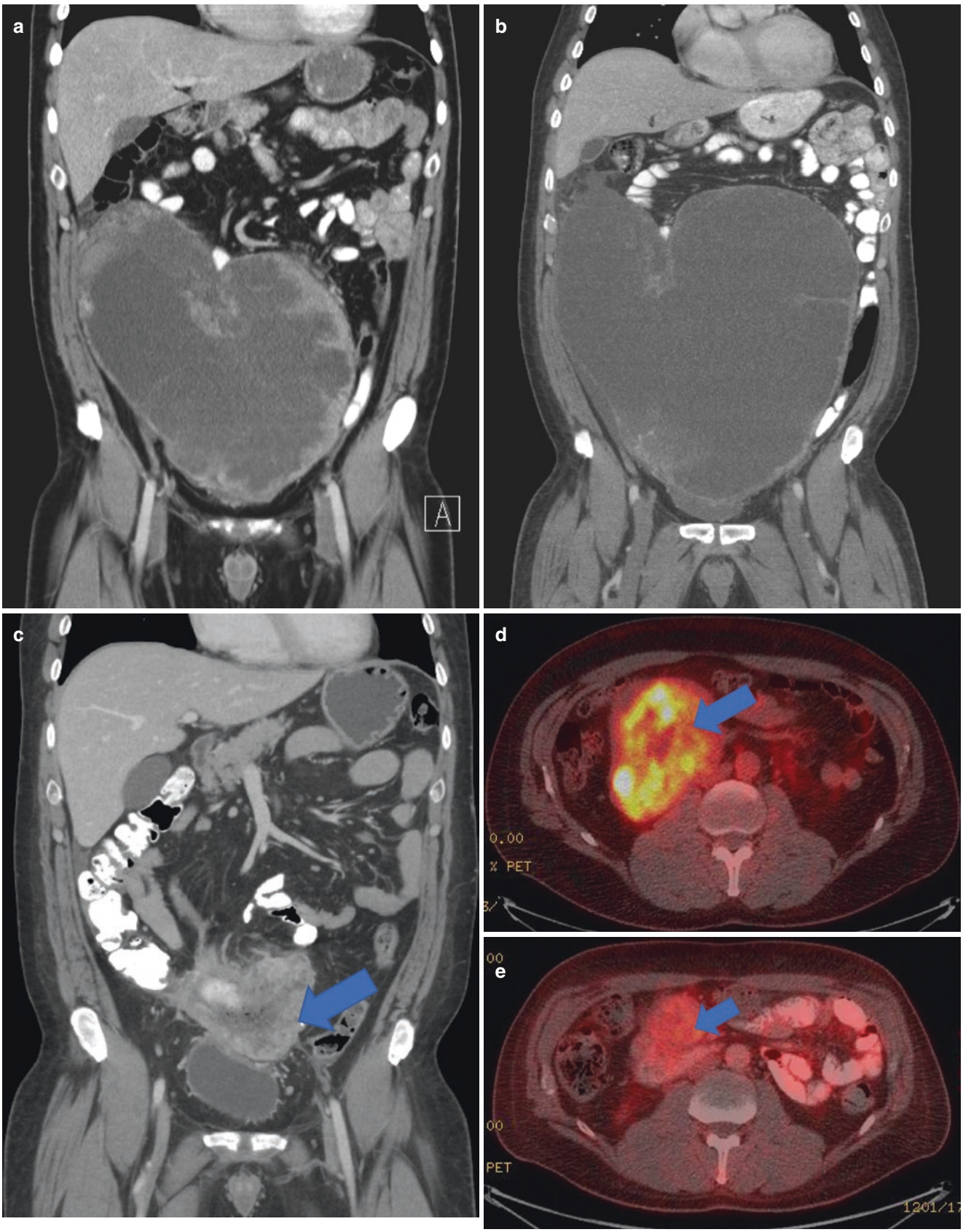


Fig. 17.1 (**a**) Baseline computed tomography (CT) scan (coronal image) of small-bowel gastrointestinal stromal tumor (GIST). (**b**) Pseudoprogression on imatinib leading to increased mass effect from the predominantly cystic mass. (**c**) Continued therapy for over a year with imatinib leading to eventual involution of the mass. Fibrosis and inflammation of the wall secondary to tumor fistulization with bowel. (**d**, **e**) Positron emission tomography (PET) CT scan images of small-bowel GIST treated with tyrosine kinase inhibitors before (**a**) and after treatment (**b**). PET CT helps in differentiating a response despite the presence of a remnant mass posttreatment (blue arrows)

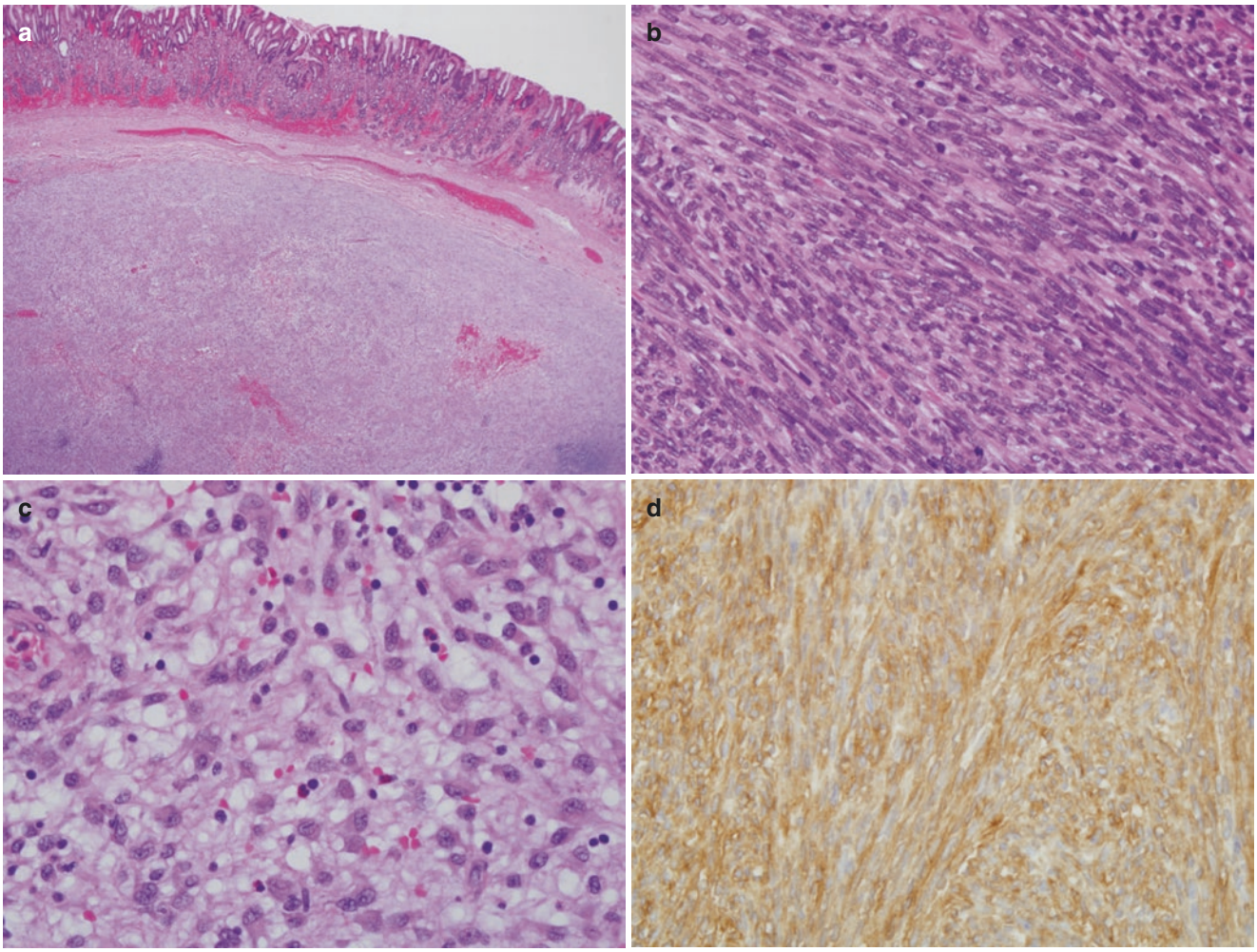


Fig. 17.2 (**a**) Low-power view of submucosal gastric gastrointestinal stromal tumor (GIST). Epithelioid features were identified on higher magnification. H& E, 2×. (**b**) High-power view of a gastric spindle cell GIST showing the characteristic elongated, spindled cells with scattered paranuclear vacuoles, and eosinophilic fibrillary cytoplasm. H &E stain, 40×. (**c**) High-power view of a gastric epithelioid GIST. H & E, 40×. (**d**) DOG-1 immunohistochemical stain shows positive membranous and cytoplasmic staining in a gastric spindle cell GIST. DOG-1 stain, 40×. (Pictures courtesy of Dr. Sherry Okun of Medical University of South Carolina)

the interstitial cells of Cajal or its stem cell precursors are the likely cells of origin of GIST [1, 2].

Molecular Classification

In approximately 85% of GISTs, the pathogenesis is linked to a mutation in the *KIT* proto-oncogene leading to constitutive activation of the receptor. The majority of the primary *KIT* gene mutations affect exon 11 (approximately 75%), coding for the juxta-membranous domain causing ligand-independent receptor activation, followed exon nine mutations (seen most commonly in intestinal GISTs) and rarely in exon 13 or 17 [44–46].

Approximately, 5% of GISTs, or 35% of GISTs lacking *KIT* mutations, have activating mutations in platelet-derived growth factor alpha (*PDGFRA*), coding for a related receptor tyrosine kinase [47, 48]. The majority of these mutations are seen in gastric GISTs and most mutations are seen in exon 18 encoding for tyrosine kinase domain 2; a few others occur in exon 12 (juxtamembrane domain) and rarely in exon 14 (tyrosine kinase domain 1) [44].

There are approximately 10–15% of GISTs that do not contain mutations in either *KIT* or *PDGFRA* and are frequently referred to as wild-type GISTs. These tumors have alternative activating pathways. Approximately, 7.5% of patients with gastric GIST have loss of function mutations in succinate dehydrogenase (*SDH*) gene subunits or loss of SDHB protein expression, known as *SDH*-deficient GIST, and most of them manifest before the age of 40 [49–53]. A key oncogenic mechanism in these tumors is a defect in energy metabolism. The most commonly mutated *SDH* subunit is *SDHA*, with an estimated frequency of 28% of all SDH-deficient GISTs. These can be seen in children as well

as adults and their spectrum of clinical behavior can vary from indolent to aggressive [54]. Typical of SDH-deficient GISTs is overexpression of insulin-like growth factor 1 receptor *(IGF1R)* gene, possibly by gene amplification [55]. As a result, IGF1R signaling is activated, and this has been investigated as a potential therapeutic target. *BRAF* exon 15 mutations (V600E) have been seen in ≤1% of GISTs, mainly in the subset with high-risk intestinal GIST that is negative for *PDGFR/KIT* mutations [56, 57]. These various primary driver mutations in GIST tend to be mutually exclusive.

Etiology

The majority of GIST cases are sporadic and only less than 5% are associated with syndromes or are familial. The report by Nishida and colleagues in 1998 was the first to identify a specific germline mutation as the cause of an inherited predisposition to GIST [58]. There are now 24 reported kindreds, the majority with germline *KIT* mutations, some with *PDGFRA* that have associated familial GIST with an autosomal dominant inheritance pattern, and the median age at diagnosis tends to be at least a decade younger than typical for sporadic GIST [59].

Neurofibromatosis Type 1 (NF1; von Recklinghausen's disease) is a complex disorder characterized by cutaneous (café au lait spots, axillary and inguinal freckling, dermal neurofibromas) and ocular (hamartomas in the iris, Lisch nodules) manifestations and a predisposition to various nervous system tumors. GISTs represent the most common gastrointestinal manifestation of NF1 and tend to be diagnosed in the fifth or sixth decade of life with a slight female predominance [60, 61]. Approximately, half of the cases, however, occur in the absence of a family history of NF1 and are presumably the result of a de novo mutation. Unlike in sporadic and familial GIST where the interstitial cell of Cajal hyperplasia is believed to be a direct consequence of constitutive KIT activation, in NF1, it might be secondary to *NF-1* haploinsufficiency [62]. The emergence of GIST is likely due to subsequent loss of heterozygosity at *NF-1* and accumulation of additional chromosomal alterations.

Carney-Stratakis syndrome is an autosomal dominant syndrome with incomplete penetrance and variable manifestation resulting from a germline mutation in a subunit of succinate dehydrogenase (SDHB, SDHC, or SDHD). Affected individuals are predisposed to developing paraganglioma, GIST, or both [63–66]. Carney-Stratakis syndrome is different from Carney's triad, which is a rare nonheritable syndrome associated with gastric GIST, paraganglioma, and pulmonary chondroma in young women [67]. Approximately, 150 cases have been reported so far [68]. GISTs associated with Carney's triad also show loss of expression of SDHB by immunohistochemistry, but associated *SDH* gene mutations have not been identified [69, 70].

Even patients with sporadic GIST (nonfamilial/nonhereditary) have been reported to have a slightly increased risk of developing clinically detectable synchronous and metachronous malignancies, including breast cancer, prostate cancer, renal cell cancer, lung cancer, melanoma, and leukemia [71–77]. More research will shed light on the genetic predisposition leading to this increased incidence of second primary cancers.

Prognostic Factors and Risk Stratification

GISTs can have variable clinical behaviors, but it is now clear from large and long-term follow-up studies that all GISTs have malignant potential [60]. Specific tumor characteristics can help predict the risk for recurrence and metastasis in patients with primary resectable GIST.

Tumor size and mitotic rate are key elements in risk stratification and formed the basis of the 2002 National Institutes of Health (NIH) consensus for risk stratification for GIST [78]. This report by Fletcher et al. categorized tumors as very low risk (<2 cm and <5 mitoses/50 high-power fields [HPF]), low risk (2–5 cm and <5 mitoses/50 HPF), intermediate (<5 cm and 6–10 mitoses/50 HPF or 5–10 cm and <5 mitoses/50 HPF), and high risk (>5 cm and >5 mitoses/50 HPF or >10 cm and any mitotic rate). This prediction scheme was validated in subsequent population studies of primary GIST recurrence [21, 79, 80]. A long-term follow-up study of more than 1600 patients formed the basis for the updated guidelines proposed by Miettinen and Lasota in 2006 for the risk stratification of primary GIST based on mitotic index, size, and anatomic location of tumor [81]. This confirmed the findings of prior smaller studies showing the importance of location in prognosis [13]. The risk of recurrence is higher for non-gastric GISTs than for gastric GISTs of the same size and mitotic count. Additional studies confirmed this risk stratification model, showing anatomic location as an independent prognostic factor and also noted that within the "high-risk" category (tumor size > 5 cm and mitotic count > 5 per 50 HPFs) one can separate a "very high-risk" category with tumor size > 10 cm and mitotic count > 5 per 50 HPFs or tumor size > 5 cm and mitotic count > 10 per 50 HPFs [22, 82, 83]. Of all the variables, the mitotic rate of >5/50 HPF remains the critical factor in predicting a high recurrence rate [84, 85].

The NCCN (National Comprehensive Cancer Network) GIST Task Force adapted the Miettinen and Lasota criteria for their report, and this remains the most widely used methods to predict risk of recurrence after resection of primary GIST (Table 17.1) [13, 22].

DeMatteo and colleagues also developed a nomogram to predict relapse-free survival at 2 and 5 years based on tumor

Table 17.1 Risk of recurrence/metastases of GIST based on tumor location, size, and mitotic rate

Site	Mitotic rate per 50 HPF	Size (cm)	Risk of progressive disease
Stomach	≤5	≤2	None (0%)
		>2 to ≤5	Very low (1.9%)
		>5 to ≤10	Low (3.6%)
		>10	Moderate (10%)
	>5	≤2	None (0%)[a]
		>2 to ≤5	Moderate (16%)
		>5 to ≤10	High (55%)
		>10	High (86%)
Duodenum	<5	≤2	None (0%)
		>2 to ≤5	Low (8.3%)
		>5 to ≤10	Insufficient data
		>10	High (34%)
	>5	≤2	Insufficient data
		>2 to ≤5	High (50%)
		>5 to ≤10	Insufficient data
		>10	High (86%)
		≤2	None
Jejunum/ Ileum	<5	>2 to ≤5	Low (4.3%)
		>5 to ≤10	Moderate (24%)
		>10	High (52%)
	>5	≤2	High (50%)[a]
		>2 to ≤5	High (73%)
		>5 to ≤10	High (85%)
		>10	High (90%)
Rectum	<5	≤2	None
		>2 to ≤5	Low (8.4%)
		>5 to ≤10	Insufficient data
		>10	High (57%)
	>5	≤2	High (54%)
		>2 to ≤5	High (52%)
		>5 to ≤10	Insufficient data
		>10	High (71%)

Adapted from Miettinen and Lasota (2006) and NCCN GIST task force report (2010) [13, 22]
HPF High-power field
[a]Small number of cases; Insufficient data: too few cases in this category

size, mitotic index, and site from 127 patients treated at one institution [86]. This was then tested and validated in patients from the Spanish Group for Research on Sarcomas (GEIS; 212 patients) and the Mayo Clinic (148 patients). The nomogram achieved a strong concordance probability, and the predictions were well calibrated. This nomogram accurately predicts recurrence-free survival (RFS) after resection of localized primary GIST, and is another useful tool in the selection of patients for postoperative imatinib therapy [87].

Tumor rupture (either at surgery or spontaneously), incomplete resection, a high Ki-67 (cellular proliferation) index, and SLITRK3 expression are also reported to impact disease-free survival and are correlated with poorer outcome [81, 88–90].

The nature of mutations in GIST has also been evaluated for their prognostic significance [91, 92]. Some studies showed that *KIT* exon 11 deletions are associated with a worse outcome. However, *KIT* exon 11 mutations can also be detected in incidental GISTs with a more benign clinical course (incidental, <1 cm tumors that are mitotically inactive) [93–95]. Variability in the prognosis has been shown depending on the type of *KIT* exon 11 mutation as well [96, 97]. In the study by Dematteo et al., *KIT* exon 11 mutations or insertions were found to be favorable; however, deletions involving codons 557–558 and *KIT* exon 9 mutations had a worse prognosis, but this was not significant on multivariate analysis [86]. In this study, *PDGFR* mutations did not correlate with outcome but in other studies *PDGFRA* mutations have been shown to be less aggressive with a lower recurrence rate as compared to those with *KIT* mutations [98, 99]. Given the conflicting data, the type of mutation is not routinely used for prognostication but has value in predicting response to tyrosine kinase inhibitor (TKI) therapy as described later in the chapter.

Treatment

While surgery remains the mainstay of curative therapy, the addition of imatinib has significantly improved progression-free survival (PFS) and overall survival (OS) in patients with localized or metastatic GIST. GISTs are resistant to conventional chemotherapy and radiation, and hence prior to imatinib, there was no effective treatment for GISTs except surgery. A simplified treatment algorithm for newly diagnosed GIST is outlined in Fig. 17.3.

Management of Localized Primary Gastrointestinal Stromal Tumor

Principles of Surgery for Localized Gastrointestinal Stromal Tumor

The goal of surgery is to perform a complete resection with an intact pseudo capsule, microscopic negative margins (R0), and minimal morbidity and visceral disruption. There are no data supporting the need for the same wide margins of resection for GISTs as there are for adenocarcinomas [100]. In general, primary tumors do not invade additional surrounding organs, despite appearances on CT scans, and may be removed with a wedge or segmental resection of the involved stomach or bowel [100]. Lymph node dissection is not generally indicated since lymph nodes are rarely involved, except in the case of an SDH-deficient gastric GIST. Lymphadenectomy should be considered, if pathologic lymphadenopathy is noted at the time of surgery. Tumor

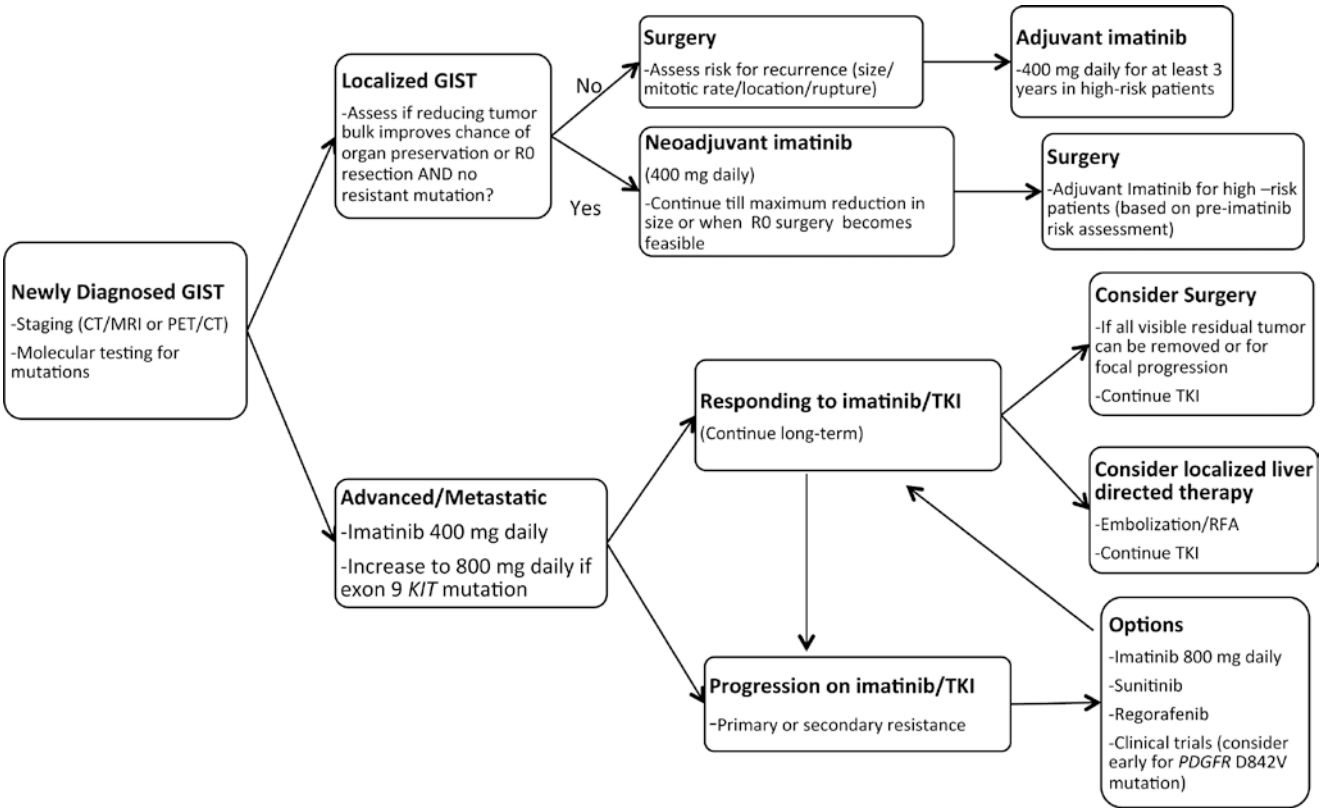


Fig. 17.3 Treatment algorithm for newly diagnosed gastrointestinal stromal tumor (GIST)

rupture at the time of surgery and positive margins has been associated with increased risk for tumor recurrence. However, in the imatinib era, patients who have had a complete resection of all macroscopic disease but still have positive microscopic margins (R1 resection) might not require re-excision and should be carefully reviewed by a multidisciplinary team of surgical oncologists, pathologists, and medical oncologists to assess the need for re-excision.

Tumors ≥ 2 cm in the stomach and any size tumors in the colon and rectum should ideally be resected, but incidental gastric GISTs that are <2 cm could be observed since their natural history is unknown and they might follow a more benign course [38]. Subcentimeter gastric GISTs have been reported in 22.5% of autopsies done in Germans >50 years old and in 35% of Japanese patients undergoing gastrectomy for gastric cancer, so clearly some of these do not become clinically relevant [101, 102]. The treating medical and/or surgical oncologist should carefully discuss the risks and benefits of surgery versus long-term observation with the individual patient. Resection should be favored if a laparoscopic approach is feasible and for all tumors that are symptomatic (e.g., hemorrhage secondary to mucosal erosions) or increase in size on follow-up (irrespective of size). Although endoscopic resection of small gastric GISTs has been reported, this increases the risk of a positive peripheral margin as these neoplasms frequently involve the muscularis propria [103].

Minimally invasive surgery (MIS; laparoscopy) and open resection (laparotomy) are the two different surgical options available for gastric GIST tumors. Laparoscopic resection is effective and safe when performed by an experienced surgeon, knowing that an R0 resection is feasible [104, 105]. Definitive prospective data comparing the two options are lacking but there are retrospective analyses, meta-analyses, and small single/multi-institutional case series comparing these two surgical approaches. A large multi-institutional retrospective analysis of 397 patients with gastric GIST undergoing either MIS (167) or open surgery (230) showed that MIS resection was associated with shorter length of stay (MIS, 3 days vs. open, 8 days) and fewer ≥ grade 3 complications (MIS, 3% vs. open, 14%) but similar recurrence-free or OS was noted (both $P > 0.05$) [106]. In a recent meta-analysis reported by Pelletier et al., the laparoscopic approach for gastric GIST patients was associated with a statistically significant shorter length of hospital stay (3.82 days; 2.14–5.49) but again no difference in recurrence rates or OS was noted [107].

For small-bowel GISTs, a laparotomy is necessary, and the abdomen should be thoroughly explored to identify and remove any previously undetected peritoneal metastatic deposits. Anatomic considerations usually dictate the type of surgery [108]. For example, large proximal gastric tumors might require a total gastrectomy, periampullary tumors may

necessitate a pancreaticoduodenectomy, and anorectal tumors at the level of the levator ani muscles may mandate an abdominoperineal resection. In the era of imatinib, however, an *en bloc* multi-organ resection is rarely required to achieve negative microscopic margins. In a meta-analysis comparing outcomes in patients with duodenal GISTs that undergo limited resection (LR; $n = 167$) versus pancreaticoduodenectomy (PD; $n = 98$), LR was associated with lower rates of distant metastases, better disease-free survival, and improved postoperative morbidity compared to PD. Similar results were seen in a retrospective analysis evaluating 114 patients with duodenal GIST treated surgically with either LR ($n = 82$) or PD ($n = 23$) with a median tumor size of 5 cm and median follow-up of 36 months. The OS and event-free survival were similar in both the groups, but LR resulted in lesser morbidity as compared to PD [109]. Hence, one should consider neoadjuvant imatinib in patients with locally advanced duodenal GISTs to see if this might make their tumor amenable to an LR over PD [110].

Adjuvant Treatment with Imatinib

With surgical resection alone for primary GIST, the rate of recurrence was as high as 85–90% for large (>5 cm) higher risk tumors and the median time to recurrence was 2 years [111–113]. Prognostic factors identified impacting on disease-specific survival included tumor size, mitotic index, complete resection without tumor rupture, and location of the primary tumor, which form the basis of the risk stratification described earlier.

Imatinib, an oral, selective, small-molecule inhibitor of *KIT, PDGFRA,* and other tyrosine kinases was approved by the US Food and Drug Administration (FDA) in 2002 for metastatic/unresectable CD 117-positive GISTs. Observing its success in advanced GIST, it was then tested in the adjuvant setting. Clinical trials, which played a pivotal role leading to the approval of imatinib in the adjuvant setting, are detailed in Table 17.2 and discussed as follows [114–118].

The first, a phase II study, by the American College of Surgical Oncology Group (ACOSOG), Z9000, enrolled 107 patients with resected GIST that were considered at high risk of recurrence: tumors ≥ 10 cm, those with evidence of rupture or hemorrhage at the time of surgical resection, or those with up to five peritoneal implants [119]. This study demonstrated that imatinib for 1 year at a daily oral dose of 400 mg was well tolerated and after a median follow-up of 7.7 years, the 1- and 5-year OS rates were 99% and 83%, respectively, and the RFS rates were 96% and 40%, respectively.

Table 17.2 Clinical trials discussing adjuvant imatinib for GIST [114–118]

	Phase	*N* and patient characteristics	Dose and duration of Imatinib	Median f/u	Outcome
ACOSOG Z9000	II	*N* = 107 Completely resected primary GIST > 10 cm, ruptured, hemorrhaging, multifocal (<5 sites)	400 mg/d × 1 year	7.7 years	1 year RFS: 96% 2-year RFS: 60% 3-year RFS: 40% 1-year OS: 99% 2-year OS: 97% 3-year OS: 83%
ACOSOG Z9001	III	*N* = 713 Completely resected, size ≥ 3 cm, KIT+	Randomized to imatinib 400 mg/d × 1 year or placebo	19.7 mo	1-year RFS: 98% vs. 83% (HR: 0.35, 95% CI 0.22 to 0.53, *P* < 0.0001) No OS benefit[a]
EORTC 62024	III	*N* = 908 Intermediate/high-risk resected GIST[b], tumor rupture, intra-op tumor spillage	Randomized to imatinib 400 mg/d × 2 years or placebo	4.7 years	3-year RFS: 84% vs. 66%, 5-year OS**:** 100% vs. 99%
SSG XVIII	III	*N* = 400 High-risk resected GIST classified as having 1 of the following: Size >10 cm Mitotic rate > 10/50 hpf Size >5 cm with >5/50 hpf Tumor rupture	Randomized to 1 year vs. 3 years of imatinib 400 mg/d	54 months	5-year RFS: 48% (1 year) vs. 66% (3 years) (HR 0.46, 95% CI 0.32 to 0.65, *P* < 0.0001) 5-year OS**:** 82% (1 year) vs. 92% (3 years) (HR 0.45, 85% CI 0.22 to 0.89, *P* < 0.019)
PERSIST – 5 (ongoing)	II/ III	*N* = 91 High risk of recurrence defined as: Size >2 cm and >5 mitosis/50 hpf Size >5 cm, non-gastric location	Imatinib 400 mg/d × 5y	34.2 months	Interim data: 85 evaluable pts 3-year RFS: 95%

Abbreviations *hpf* high-power field, *OS* Overall survival, *RFS* Relapse-free survival, *SSG* Scandinavian Sarcoma group, *pts* patients

[a]Reason for likely no OS benefit: quick crossover to the treatment arm for recurrence

[b]Based on NIH 2002 classification (based on tumor size and mitotic rate)

A subsequent phase III double-blind trial (ACOSOG Z9001), of imatinib 400 mg daily versus placebo with crossover, enrolled patients with resected KIT-positive GIST tumors larger than 3 cm [115]. Accrual was stopped early after 713 patients were randomized, based on a pre-planned interim analysis showing significant benefit in 1-year RFS in the adjuvant imatinib arm of 98% vs. 83% in the placebo arm (HR: 0.35; 95% CI: 0.22–0.53; 1-sided $P < 0.0001$). No difference in OS was observed between the two arms.

The Scandinavian Sarcoma Group study, SSGXVIII, evaluated 1 year versus 3 years of adjuvant imatinib in GIST patients with at least one high-risk feature; >10 cm longest diameter, mitotic count >10 mitoses per 50 HPFs, tumor diameter > 5 cm and mitotic count > 5 per 50 HPFs, or tumor rupture before surgery or at surgery. After 54 months of follow-up, the 5-year RFS was significantly higher in the 3-year versus 1-year group (65.6% vs. 47.9%; HR: 0.46; 95% CI: 0.32–0.65; $P < 0.0001$) and so was the 5-year OS (92.0% vs. 81.7%; HR: 0.45; 95% CI: 0.22–0.89; $P = 0.019$) [116]. This study also noted that imatinib offered additional protection for 1 year after cessation, following which rates of relapse were similar to historical controls.

Retrospective analyses looking at the effect of molecular correlates on adjuvant therapy show that patients with *KIT* exon 11 mutations appear to benefit the most, with limited benefit in the other groups (i.e., exon 9 mutation) from adjuvant imatinib, but the numbers of these patients were small [116, 120].

Based on the SCGXVIII study, in 2012, the U.S. FDA updated the initial 2008 adjuvant imatinib approval, consistent with the current recommendation of the NCCN guidelines for at least 36 months of adjuvant imatinib therapy for intermediate- to high-risk patients [38, 116]. The optimal duration of adjuvant therapy has not yet been determined, and PERSIST-5 is currently exploring the option of a total of 5 years of imatinib in the adjuvant setting for high-risk patients. Reports from their planned 3-year interim analysis were favorable, confirming high rates of RFS [114]. Given the favorable toxicity profile of imatinib, experts believe that high-risk patients should continue on lifelong imatinib, taking into consideration individual life expectancy and tolerance to therapy. On the other hand, one might consider following a close surveillance pathway with introduction of imatinib at the first sign of recurrence to help identify those who need lifelong imatinib.

Recommended follow-up for completely resected tumors is every 3–6 months for 5 years with history and physical examination, labs, and radiological imaging, and then annually until 10 years. The risk of recurrence and use of adjuvant therapy should also be taken into consideration, with closer follow-up recommended after cessation of adjuvant imatinib.

Neoadjuvant Treatment with Imatinib

The main goal for using imatinib in the neoadjuvant setting is allowing organ preservation and reducing tumor bulk allowing for complete surgical resection. Other considerations for using neoadjuvant imatinib are detailed in Table 17.3 [88, 121, 122].

There are a few retrospective studies reporting the benefits of neoadjuvant imatinib, but the RTOG 0132/ACRIN 6665 trial was the first prospective study evaluating the use of imatinib in the neoadjuvant setting [123, 124]. This phase II trial evaluated the efficacy of imatinib 600 mg/day in patients with resectable primary (≥5 cm) or recurrent GIST (≥2 cm) for 8–12 weeks prior to planned surgical resection, and those with partial response (PR) or stable disease (SD) were eligible for adjuvant imatinib for 2 years at the same dose. Among the patients with primary GIST, 90% demonstrated an objective response prior to surgery, and 92% subsequently underwent R0/R1 resections. The estimated 2-year RFS was 83%, which compares favorably with the 2-year RFS of 73% from the ACOSOG Z9000 trial of adjuvant imatinib for 1 year. Long-term follow-up suggested that approximately one-third (36%) patients with primary GIST ≥ 5 cm experienced a recurrence, and in most of them, this occurred after discontinuing imatinib [124].

Recently, the European Organization for Research and Treatment of Cancer (EORTC) published its pooled analysis of 161 patients with locally advanced, nonmetastatic GIST treated with neoadjuvant imatinib for a median time of 40 weeks. Postoperative imatinib was resumed in patients regardless of their surgical margins for a duration of at least 2 years, side effects profile permitting. They show a favorable 5-year disease-specific survival and RFS of 95% and 65%, respectively [125].

The ideal duration of neoadjuvant imatinib is not well studied but data from trials of advanced GIST demonstrated that maximal radiographic response to imatinib generally required 6–9 months of treatment and signs of progression usually occur after 10–12 months of treatment [126]. Consequently, at many institutions, the duration of neoadjuvant therapy is individualized depending on the need for organ-preserving surgery, and imatinib may be administered as long as continued radiographic response is observed

Table 17.3 Situations to consider neoadjuvant imatinib[a]

1. Borderline resectable or unresectable locally advanced GIST
2. Resectable GIST requiring extensive organ disruption
3. Esophageal, gastric-esophageal junction, duodenum, and rectal GIST for potentially sphincter-sparing and esophageal-sparing surgeries [88, 121, 122][b]
4. Locally recurrent GIST or locally confined resectable metastatic GIST

[a]No definitive consensus for time to start and duration of treatment
[b]Based on case reports

[88, 121, 122]. Preoperative imatinib can, however, interfere with the accurate assessment of the risk for recurrence, and the optimal length of postoperative imatinib therapy in this setting remains undefined.

Management of Advanced Disease-Frontline Therapy

Prior to the discovery of *KIT* activating mutations in GIST leading to the use of imatinib, the prognosis and treatment options for metastatic GIST were dismal with a median survival of 5–12 months [112, 113]. In the era of TKIs, the median OS of patients with advanced GIST has increased to approximately 60 months [127]. In this section, we discuss the treatment considerations for patients presenting with metastatic GIST. Table 17.4 lists the major trials establishing the dose and duration of imatinib for frontline therapy [127–133].

Dosing and Duration of Imatinib

Imatinib, a multitargeted TKI has demonstrated significant benefit in patients with metastatic GIST in many phase I, II, and III clinical trials (Table 17.4). The B-2222 study was one of the initial studies showing an improved median survival from 20 to 60 months in patients treated with imatinib with similar overall response rate (ORR) and time to progression (TTP) in patients treated with imatinib 400 mg versus 600 mg daily [127]. An extended follow-up (median 9.9 years) of patients enrolled in this phase II study showed that the 9-year OS rate for all patients was 35%, 38% for those with complete response (CR) or PR, 49% for those with SD, and 0% for progressive disease (PD). Low tumor bulk at baseline predicted for longer TTP and improved OS [134].

Two large phase III randomized trials, the EORTC 62005 (n = 946, median f/u: 760 days) and CALGB 150105 (n = 746, median f/u: 4.5 years), tested the efficacy and of imatinib 400 mg daily versus 800 mg daily in patients with metastatic/unresectable GIST [131, 132, 135]. There were no differences noted between the two doses in terms of OS, ORR, and PFS, but there was significantly more toxicity noted in the high-dose arm. Crossover was allowed in both the studies to the higher dose arm when patients progressed on 400 mg daily. A meta-analysis of both these trials concluded that the presence of a *KIT* exon 9 mutation was the only significant predictive factor for benefit from higher doses in terms of PFS (HR of 0.58, 95% CI; 0.38–0.91) and

Table 17.4 Prospective clinical trials evaluating benefit of imatinib in metastatic GIST

Study	Phase	Number of patients	Dose of imatinib (n)	Outcomes (%)	Comments
van Oosterom et al. [128]	I	35	400 mg/d 300 mg BID 400 mg BID 500 mg BID	PR: 54 SD: 37	MTD was 400 mg BID Dose-limiting toxicities were severe nausea, vomiting, edema, and rash
US B2222 [127, 129]	II	147	400 mg/d (73) vs. 600 mg/d (74)	CR: 0 vs. 3 PR: 69 vs. 65 SD: 14 vs. 18	No statistically significant difference in response, PFS, OS, or toxicity between the two doses. Median OS - 57 months
EORTC [130]	II	27	400 mg BID	CR: 4 PR: 67 SD: 18	
EORTC 62005 [131]	III	946	400 mg/d (473) vs. 400 mg BID (473)	CR: 5 vs. 6 PR: 45 vs. 48 SD: 32 vs. 32	PFS favored 400 mg BID (P = 0·026), but no difference in OS More dose reductions and treatment interruptions were associated with the higher dose Crossover to higher dose was allowed at progression with benefit.
Intergroup SO033 [132]	III	746 (694 eligible)	400 mg/d (345) vs. 400 mg BID (349)	CR: 5 vs. 3 PR: 40 vs. 42 SD: 25 vs. 22	No statistically significant difference in PFS (18 vs. 20 months) and OS (55 months vs. 51 months) Crossover to higher dose was allowed at progression with benefit
BFR14 [133]	III	58	400 mg/d interrupted (32) 400 mg/d ongoing (26)	PD: 81 vs. 31 PFS: 6 months vs. 18 months	182 patients with advanced GIST were enrolled, and 58 patients with PR or SD at 1 year were randomly assigned to interrupt therapy vs. continue imatinib. No differences in OS or imatinib resistance were observed between the two arms

Abbreviations: *BID* twice daily, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *PFS* progression-free survival, *OS* overall survival, *EORTC* European Organization for the Research and Treatment of Cancer, *MTD* maximum tolerated dose

ORR (47% vs. 21%, $P < 0.0037$), but no difference in the OS [136]. In conclusion, imatinib 400 mg daily is the recommended starting dose, but dose escalation to 800 mg daily is advised for patients with *KIT* exon 9 mutations or after disease progression on the lower dose.

In another randomized control trial, the BFR14 study, patients with advanced GIST who had SD or better after 1 year on imatinib were randomized to either continue imatinib until disease progression or treatment was interrupted with reintroduction of imatinib at the time of progression. Of the 58 patients, 32 were randomized to the interrupted (INT) group and 26 in the continuous (CONT) group. The rate of progression (31% vs. 81%) was lower and the PFS (18 months vs. 6 months; $P < 0.0001$) was significantly better in the CONT group, but a majority of patients responded to reintroduction of imatinib [133]. A follow-up to this study reported on 71 patients who had SD or better at 1 year ($n = 32$), 3 years ($n = 25$), and 5 years ($n = 14$) was randomized to the INT group. Fifty-four patients out of 71 progressed off treatment, with progression noted at the known sites of disease as well as new lesions. Imatinib was reintroduced in 51 patients, but resulted in disease control only in a fraction of patients who had initial response to treatment (8/19 had a repeat CR and 12/23 had a repeat PR after restarting imatinib). Patients progressing rapidly after interruption had a poorer prognosis and appeared to develop secondary resistance faster [137]. Hence, at the current time, continuation of imatinib until progression or unacceptable adverse effects is recommended.

Imatinib is metabolized in the liver by CYP450 3A4; therefore, one must be cautious of the drugs and foods inhibiting or inducing this enzymatic pathway. Common side effects while on imatinib are fluid retention, usually presenting as peripheral edema or periorbital edema, nausea, diarrhea, abdominal pain, myalgia, muscle cramps, anemia, fatigue, and skin rash. The majority of these adverse effects tend to be mild (National Cancer Institute Common Toxicity Criteria Adverse Events [NCI CTCAE] grade 1 or 2) and tend to improve with prolonged therapy [38]. At times, there may be fluid retention causing pleural/pericardial effusion or ascites that may be symptomatic and require temporary or permanent discontinuation of treatment. Serious adverse events have been reported (<5%) in the form of liver function abnormalities, lung toxicity, bone marrow suppression causing neutropenia, and myelodysplastic syndrome, requiring discontinuation or dose reduction. Severe gastrointestinal bleed or intratumoral bleeding can occur in responding patients, especially during the initial months of treatment, requiring supportive care and might require temporary discontinuation of imatinib. Cardiotoxicity has also been rarely noted with long-term use of imatinib in the form of arrhythmias, acute coronary syndrome, and heart failure [138, 139].

Mutational Status Is Predictive of Response to Imatinib

Analysis of mutational status of GIST samples from these trials has provided valuable information regarding the correlation between response and the type of driver mutations, and the cause for primary and secondary resistance to imatinib.

In the multicenter US–Finland collaborative study (B2222 phase II study), patients with *KIT* exon 11 mutations had higher PR (83.5% vs. 48%), event-free survival, and OS as compared to those with exon 9 mutations or patients with wild-type GIST [38, 132, 140].

The aforementioned EORTC 62005 study and the CALGB 150105 study confirmed the improved tumor response in patients with *KIT* exon 9 mutations treated with 800 mg daily compared to 400 mg daily [132, 136]. However, it is important to note that tolerance to the 800 mg dose is much better, with fewer side effects when the dose is escalated from 400 mg over a 4–8 week period [135].

GISTs harboring a *PDGFRA* exon 18 D842V mutation or other mutations in the same exon 18 locus are insensitive to imatinib and other available TKIs, and this observation has been noted in preclinical models and prospective and retrospective studies [141, 142]. The median PFS in patients with the *PDGFRA* D842V mutation is 2.8 months compared to 28.5 months for patients with other *PDGFRA* mutations.

Assessing Response to Therapy

Patients with advanced unresectable disease should get imaging with either a CT scan or MRI of the abdomen and pelvis (CT chest only if initial staging scans reveal metastases) or a PET/CT at baseline prior to beginning treatment and then at 3 months or earlier if needed, to determine response to treatment [38]. Decreased tumor density or decrease in the FDG avidity on PET are early indicators of response to treatment and can serve as a tool for early detection of primary resistance to imatinib treatment. A small prospective study looked at dynamic CT or PET/CT response after a short duration of neoadjuvant imatinib 600 mg daily for either 3, 5, or 7 days in 19 patients. Response rate was 69% by PET/CT scan and 71% by dynamic CT scan, but there was no difference in cytoreduction seen between 3 and 7 days of treatment [143]. A decrease in size of the tumor is noticed at a later stage; in fact, in some cases the size of the tumor may even increase (pseudoprogression) initially secondary to intratumoral hemorrhage and or degeneration [144, 145]. These are the few clinical scenarios where a PET scan might be useful if the response on CT is ambiguous due to pseudoprogression and inability to assess the change in density [39, 41, 146].

Given this response pattern, using standard RECIST (Response Evaluation Criteria in Solid Tumors) will underestimate response. Choi criteria have been proposed for assessing response to imatinib in GIST patients that take into consideration tumor density in addition to size and correlate better with TTP and disease-specific survival [147].

For patients who have initial response and then develop secondary resistance, two forms of progression can occur. One is more diffuse progression and easier to identify on imaging, but the other form of progressive disease is the "nodule within a mass" pattern, which is the development of a solid peripheral nodule(s) within a previously responding hypodense tumor. This focal progression represents expansion of a resistant clone of tumor cells and often a forerunner of more diffuse tumor progression, and if detected early might be amenable to localized therapy [148].

Surgery and Other Local Therapy for Advanced/Metastatic Gastrointestinal Stromal Tumors

Metastasectomy should be considered for solitary metastases or limited metastatic disease, and studies suggest favorable long-term disease control and OS compared to systemic therapy alone [126, 149–156]. Benefit was noted even in the pre-imatinib era, when patients with liver as the only site of recurrence/metastases (approximately 67% of patients) underwent liver resections with a 5-year survival rate of 27–34% [113, 157].

In theory, resection of residual disease may decrease tumor burden and might delay or prevent the development of resistant clones prolonging the time to disease progression. A retrospective study recently published analyzed the benefit of surgery on survival in patients with metastatic, locally advanced, or recurrent GIST sensitive to imatinib at 14 centers in Spain [156]. A total of 171 patients were evaluated and divided into two cohorts: Cohort A that continued on imatinib after PR/SD and Group B was treated with metastasectomy after PR/SD was achieved and also continued on imatinib treatment. The median follow-up time was 56.6 months. The median survival was 59.9 months in Cohort A and 87.6 months in Cohort B, which was statistically significant [156].

Other studies have also shown that the group that benefits the most from cytoreductive surgery are patients still responding to TKI therapy at the time of surgery and the selection of these patients should be on a case-by-case basis [150]. However, in the absence of a randomized clinical trial, it is unclear if the prolonged survival in patients benefiting from imatinib is a matter of selection bias. It is clear, however, that patients with generalized progression do not appear to benefit from surgery and are best treated with switching TKI therapy.

In case of unresectable liver metastases (either due to number and location) or presence of disease outside of the liver with focal progression in the liver, interventional techniques might be utilized to enhance the benefit from TKIs. Hepatic arterial bland embolization, chemoembolization, and radiofrequency ablation have all been utilized with radiologic response or disease stabilization in most patients with imatinib resistance manifesting as progressive liver metastases [158–161].

Management of Imatinib Resistance Second-Line Therapy and Beyond

Primary resistance to imatinib is defined as evidence of clinical progression during the first 6 months or at the first set of scans (usually first 3–4 months). This is typically seen in GISTs with *PGDFRA* exon 18 D842V mutations and some cases with *KIT* exon 9 mutations when treated with imatinib 400 mg daily, and majority of cases with *SDH*-deficient GIST [38, 140, 162, 163].

Secondary resistance is defined as disease progression after the patient was noted to have sustained objective response or disease control with imatinib. This usually occurs secondary to overgrowth of a clone with primary imatinib resistance or development and progression of a clone with secondary activating *KIT* (usually in exon 13 or 17) and *PDGFRA* mutations or due to acquired pharmacokinetic variability [148, 164–166].

Following development of primary or secondary resistance with documented disease progression on imatinib 400 mg daily, consideration should be given for dose escalation to 800 mg daily, especially for patients with KIT exon 9 mutations. Next line of treatment would involve switching therapy to sunitinib.

Sunitinib

Sunitinib is a small-molecule inhibitor targeting PDGFR, vascular endothelial growth factor receptors (VEGFR), *KIT*, *RET*, *CSF-1R*, and *FLT3*. Currently, this is the standard of care as next-line therapy in patients who have failed imatinib [38]. It was granted FDA approval for this indication in 2006 after the efficacy, safety, and clinical benefit were demonstrated in a randomized phase III placebo-controlled study [167]. Patients with GIST that were either intolerant or progressed while on imatinib were randomized in a 2:1 fashion to receive either sunitinib ($n = 207$) or placebo ($n = 105$) at a dose of 50 mg/day for a 6-week cycle (4 weeks on and 2 weeks off). A planned interim analysis revealed a statistically significant difference in the primary endpoint of median TTP; 27.3 weeks with sunitinib versus 6.4 weeks with placebo ($P < 0.0001$; hazard ratio = 0.33). PFS and OS were also significantly improved in patients who received sunitinib, but OS benefit lost significance with longer follow-up. Partial response was 7% and

stable disease 58% in the sunitinib group compared with 0% and 48%, respectively, in the placebo group.

A daily dosing regimen was also tested in a Phase II study testing 37.5 mg of sunitinib daily for 28 days in patients with GIST following imatinib failure, due to concerns of disease flare noted during the treatment breaks. This study confirmed effective drug concentrations throughout the cycles with no additional drug accumulation. The side effect profile was similar to the intermittent dosing schedule. At 6 months, response rates were comparable to the intermittent dosing regimen with an ORR of 53% (13% PR, 40% SD). The median PFS and OS were 34 weeks and 107 weeks, respectively. Results from this study suggest that continuous daily dosing is as effective a dosing strategy as the intermittent dosing schedule [38, 168]. Thus, in the second-line setting, sunitinib can be used either as a 50-mg/day in intermittent dosing schedule or as a 37.5 mg/day continuous schedule.

Activity of sunitinib is also influenced by specific mutations. Clinical benefit has been observed with sunitinib for patients with *KIT* exon 9, *KIT* exon 11, and wild-type *KIT/PDGFRA* mutations. In the post-imatinib setting, the clinical benefit rate, PFS and OS, is higher in the group with *KIT* exon 9 and wild-type GIST compared to *KIT* exon 11, due to acquired secondary mutations. Sunitinib has shown activity against GISTs with secondary *KIT* exon 13 or 14 mutations but not against secondary mutations in *KIT* exons 17 or 18 [163]. Similar to imatinib, *PDGFRA* D842V mutations confer resistance to sunitinib as well.

Adverse events with sunitinib are in general more prevalent compared to imatinib and are mostly due to its broader targeting of TKs. Common adverse effects (mostly NCI CTCAE grade 1 and 2) seen in ≥10% of patients include fatigue, diarrhea, mucositis, skin discoloration, acral erythema, nausea/vomiting, and altered taste. These are best managed with supportive care, temporary withdrawal, or with dose reduction. Hand and foot syndrome is seen frequently and patients need to be monitored closely for this at every visit. Due to its activity against VEGFR, its additional side effects include hypertension, poor wound healing, bleeding/thrombosis, rare cases of osteonecrosis of the jaw, and proteinuria/renal toxicity. Cardiotoxicity, with decrease in left ventricular ejection fraction, has also been reported with prolonged use. Lab abnormalities in the form of hypothyroidism (approximately 4% of cases and TSH needs to be checked regularly) and reversible erythrocytosis have been associated with sunitinib [38, 169].

Regorafenib

The prognosis of patients that progressed on imatinib and sunitinib was dismal with minimal benefit from other TKIs, including sorafenib, nilotinib, and dasatinib [170–179]. Regorafenib was approved for advanced GIST patients after progression/intolerance to imatinib and sunitinib in February of 2013. This is also a multikinase inhibitor with activity against *VEGFR, KIT, TIE-2, PDGFR-β, FGFR-1, RET, RAF-1, BRAF*, and p38 MAP kinase. Efficacy in refractory patients was first established in a phase II trial of 34 patients and later was confirmed in a phase III randomized placebo-controlled trial [180, 181]. Patients with metastatic, unresectable GIST, heavily pretreated, intolerant to, or progressed on imatinib and sunitinib were randomized to either regorafenib plus best supportive care ($n = 133$) or placebo ($n = 66$) and crossover was allowed. Regorafenib (160 mg once daily for days 1–21 of a 28-day cycle) proved to be superior with a statistically significant PFS (4.8 vs. 0.9 months; $P < 0.0001$) and disease control rate (PR + SD > 6 months) (53% vs. 9%) compared to placebo. The benefit in PFS with regorafenib was observed across the prespecified patient subgroups defined by various baseline factors, including patients receiving three or higher lines of therapy and primary mutation category (*KIT/PDGFR*/wild-type). Crossover was allowed and 85% of patients from the placebo group went on to receive regorafenib due to progressive disease. There was no statistically significant difference in OS between the groups (HR 0·77, 95% CI 0·42–1·41; $P = 0·199$).

Most frequently seen adverse events of any grade were hand–foot syndrome (56%). Grade 3 or higher drug-related adverse events occurred in 61% of patients, including hypertension (23%), hand–foot syndrome (20%), and diarrhea (5%). Dose modifications were required in 72% of patients.

Reintroduction of Previous TKI Therapy

After progression on imatinib, sunitinib, and regorafenib, most patients will cycle through other available TKIs (nilotinib, sorafenib, dasatinib, ponatinib, masitinib, and/or pazopanib), but benefit is marginal with these agents in the setting of disease resistant to approved TKIs [170–179]. It is known that terminating the TKI at the time of disease progression can lead to more rapid progression in GIST patients. Hence, in the absence of a reasonable clinical trial option, there is data supporting continuing the TKI through progression or the reintroduction of a previously used TKI with prolonged duration of benefit in the palliative setting [182, 183]. In a randomized trial, patients who had previously benefited from first-line imatinib (initial disease control for ≥6 months) but now have metastatic or unresectable GIST unresponsive to at least imatinib and sunitinib were randomized to receive only imatinib ($n = 41$) or placebo ($n = 40$). The median follow-up was 5.2 months, and the PFS was double in the rechallenge group compared to the placebo group (1.8 vs. 0.9 months, HR = 0.46; $P < 0.005$). Even though the duration of response was significantly longer compared to placebo, this was brief due to the overgrowth of TKI-resistant clones [184].

Conclusion

New Therapeutics and Future Directions

Multiple other TKIs (nilotinib, sorafenib, dasatinib, pazopanib, masitinib, crenolanib, vatalanib, and ponatinib) have been evaluated in GIST patients with some activity, but once the GIST cells become resistant to multiple lines of therapy, clinical benefit from these agents is limited [170–179]. Nilotinib, a second-generation TKI, at 400 mg orally twice daily, has been studied both as a single agent in the first-, second-, and third-line setting and in combination with imatinib with no significant benefit in imatinib-resistant GIST [185–188]. Sorafenib, an RAF kinase inhibitor that also inhibits *KIT, PDGFR, VEGFR*-2, and *VEGFR*-3, has demonstrated single-agent activity (PR 13%, SD 55%) at an oral dose of 400 mg twice daily in the third- and fourth-line setting [170, 189]. Dasatinib—a kinase inhibitor against *BCR-ABL*, SRC family (*SRC, LCK, YES, FYN*), *KIT, EPHA2*, and *PDGFRB*—was tested at an oral dose of 70 mg twice daily, and though active in imatinib- and sunitinib-resistant GIST, the duration of benefit was limited [175]. Masitinib—which targets *KIT, PDGFR*, and fibroblast growth factor receptor 3 (*FGFR3*), and with known activity in imatinib naïve GIST—was tested at a dose of 12 mg/kg/day in a randomized trial compared to sunitinib (50 mg daily, 4 weeks on 2 weeks off) showing comparable efficacy and lower toxicity in the second-line setting [177, 190]. Vatalanib targets *KIT*, *PDGFR, VEGFR*-1, and *VEGFR*-2, and showed marginal benefit (PR 4%, SD 36%) in GIST patients in the second- and third-line setting in a phase II trial [191]. Ponatinib—another multitargeted TKI against *BCR-ABL, FLT3, RET, KIT, FGFR, PDGFR*, and *VEGFR*—has shown preclinical activity against major clinically relevant *KIT* mutants and refractory GIST with exon 17 activation loop secondary mutations, but further development was halted due to risk of arterial thrombotic events and hepatotoxicity seen in leukemia patients [192]. Crenolanib has shown potent inhibition of imatinib-resistant *PDGFRA* kinases associated with GIST, including the *PDGFRA* D842V mutation in several cell lines. Based on activity seen in the phase II trial, a phase III clinical trial of this agent to treat GIST with the *PDGFRA* D842V mutation is ongoing [193]. The last two years have seen an advancement in TKIs that effectively target a broader range of KIT/PDGFRA mutations [194]. Avapritinib (BLU-285), a potent and highly selective inhibitor of mutated KIT and PDGFRA, showed substantial clinical activity in GIST patients, in the phase I trial including patients with PDGFRA D842V-driven GIST and fourth-line GIST, where there are currently no effective therapies. In 56 patients with PDGFRA- driven GIST the ORR was 84% (95% CI, 71.7%-92.47%); 9% had a CR and 75% showed PR. The 12-month PFS rate was 81.2%. In 109 patients receiving avapritinib at doses of 300 or 400 mg in the fourth line or later, the ORR was 20% (95% CI, 13.1%-29.0%); 1% had a CR, 19% had a PR, and 40% had SD. The randomized phase III trial designed to test the safety and clinical activity of avapritinib vs regorafenib is currently enrolling patients with advanced GIST who have progressed on imatinib and up to two other TKIs (NCT03465722). Avapritinib was in general well tolerated, with grade 3 or 4 treatment-related AEs (TRAEs) occurring in ≥2% being anemia, periorbital edema, fatigue, hypophosphatemia, increased bilirubin, decreased white blood count/neutropenia, and diarrhea. Of note, reversible grade ½ cognitive imapirement, particularly short-term memory loss, was reported for 26% of all patients. Ripretinib (DCC-2618), is a pan-KIT/PDGFRA switch-control inhibitor, showing encouraging activity in patients across a broad range of TKI treatment-emergent mutations, in heavily pretreated GISTs in a phase 1/2 trial. Preliminary results reported for this trial showed a median PFS of 42 weeks in the second line, 40 weeks in the third-line and 24 weeks in the fourth line using doses of ≥100 mg daily, with majority showing an early metabolic response. Grade 3/4 adverse events were rare and included hypertension, anemia, diarrhea, electrolyte changes, abdominal and back pain as well as asymptomatic increase in lipase. There is also a potential increase in incidence of squamous-cell skin carcinoma. As part of this phase 1/2 trial, both tissue and liquid biopsies were performed and tested via next-generation sequencing (NGS). The NGS of plasma cfDNA revealed a reduction of mutation allele frequency (MAF) in KIT exons 9, 11, 13, 14, 17, and 18. The phase III placebo-controlled trial of DCC-2618 in fourth-line and beyond, with rapid crossover to the drug arm in case of progression, has just been completed and a second a second-line phase III randomized trial comparing the efficacy and toxicity of DCC-2618 to sunitinib in patients whose tumors have progressed on imatinib is underway (NCT03353753, NCT03673501).

Recently, NTRK fusions have been reported in GIST patients, with significant benefit seen on a phase I trial with a TRK inhibitor [195]. Some other novel targets that have been explored in clinical trials in GIST include inhibitors of the heat shock protein-90, the molecular chaperone required for the stability of *KIT* and *PDGFRA* oncoproteins, HDAC inhibitors, mTOR inhibitors, and specifically in wild-type GIST, the insulin-like growth factor 1 receptor (IGF-1R) inhibitors [196–199]. Additional promising strategies to overcome resistance include cycling the various TKIs to delay emergence of a resistant clone and combining agents with imatinib either for broader kinase inhibition or for inhibition of a downstream target in the signal transduction cascade. Chi and colleagues identified transcription

factor *ETV1* as necessary for GIST growth and survival, and since *ETV1* is activated downstream of *KIT* via the *MAPK* pathway this has led to an ongoing clinical trial combining a MEK inhibitor with imatinib [200]. *P13K/AKT/PTEN* pathway essential to oncogenic signaling downstream of KIT, and preclinical data suggest that GDC-0941, an orally bioavailable *PI3K* inhibitor, in combination with imatinib has superior antitumor efficacy in comparison to standard treatment, resulting in sustained effects even after treatment withdrawal [201].

The role of immunotherapy in GIST is at present unknown. A small clinical trial combining peginterferon α(alpha)-2b with imatinib for treatment of locally advanced/metastatic GIST patients with the rationale that peginterferon α(alpha)-2b can promote antitumor immunity showed promising results [202]. A phase I trial with ipilimumab and dasatinib in GIST patients was not found to be synergistic, and future trials are required to determine if checkpoint inhibitors (anti-CTLA4 and/or anti-PD-1/PDL-1) will have a role in GIST patients [203].

References

1. Wang L, Vargas H, French SW. Cellular origin of gastrointestinal stromal tumors: a study of 27 cases. Arch Pathol Lab Med. 2000;124(10):1471–5.
2. Sircar K, Hewlett BR, Huizinga JD, Chorneyko K, Berezin I, Riddell RH. Interstitial cells of cajal as precursors of gastrointestinal stromal tumors. Am J Surg Pathol. 1999;23(4):377–89.
3. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (gipact): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of cajal. Am J Pathol. 1998;152(5):1259–69.
4. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992–2000. Am J Gastroenterol. 2005;100(1):162–8.
5. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459–65.
6. Anonymous. Us population data from the us census bureau. www.censusgov/popest/states/NST-ann-esthtml. 2008. Accessed 8 Mar 2016.
7. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomark Prev. 2015;24(1):298–302.
8. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by sti 571, a selective tyrosine kinase inhibitor. Blood. 2000;96(3):925–32.
9. Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ, et al. Abl protein-tyrosine kinase inhibitor sti571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther. 2000;295(1):139–45.
10. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. Am J Surg Pathol. 2000;24(2):211–22.
11. Miettinen M, Sobin LH. Gastrointestinal stromal tumors in the appendix: a clinicopathologic and immunohistochemical study of four cases. Am J Surg Pathol. 2001;25(11):1433–7.
12. Takahashi Y, Noguchi T, Takeno S, Uchida Y, Shimoda H, Yokoyama S. Gastrointestinal stromal tumor of the duodenal ampulla: report of a case. Surg Today. 2001;31(8):722–6.
13. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23(2):70–83.
14. Lasota J, Carlson JA, Miettinen M. Spindle cell tumor of urinary bladder serosa with phenotypic and genotypic features of gastrointestinal stromal tumor. Arch Pathol Lab Med. 2000;124(6):894–7.
15. Lee CH, Lin YH, Lin HY, Lee CM, Chu JS. Gastrointestinal stromal tumor of the prostate: a case report and literature review. Hum Pathol. 2006;37(10):1361–5.
16. Miettinen M, Monihan JM, Sarlomo-Rikala M, Kovatich AJ, Carr NJ, Emory TS, et al. Gastrointestinal stromal tumors/smooth muscle tumors (gists) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol. 1999;23(9):1109–18.
17. Peerlinck ID, Irvin TT, Sarsfield PT, Harington JM. Gist (gastrointestinal stromal tumour) of the gallbladder: a case report. Acta Chir Belg. 2004;104(1):107–9.
18. Abou Al-Shaar H, Solimanie S, Azzam A, Amin T, Abu-Zaid A. Gastrointestinal stromal tumor of the adrenal gland: a case report and review of the literature. Endocr Pathol. 2015;26(1):27–32.
19. Bertulli R, Fumagalli E, Coco P, Messina A, Morosi C, Dileo P, et al., editors. Unusual metastatic sites in gastrointestinal stromal tumor (gist). In: ASCO annual meeting proceedings; 2009.
20. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch Int J Pathol. 2001;438(1):1–12.
21. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. Cancer. 2005;103(4):821–9.
22. Demetri GD, Von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, et al. Nccn task force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Cancer Netw. 2010;8(Suppl 2):S-1–S-41.
23. Choti MA, et al. Gastrointestinal Stromal Tumors (GISTs), emedicine.medscape.com/article/278845-overview, Accessed 12 Dec. 2016. 23 Sept 2016.
24. Chou F-F, Eng H-L, Sheen-Chen S-M. Smooth muscle tumors of the gastrointestinal tract: analysis of prognostic factors. Surgery. 1996;119(2):171–7.
25. Jasti P, Lakhani V, Woodworth A, Dahir K. Hypercalcemia secondary to gastrointestinal stromal tumors: parathyroid hormone-related protein independent mechanism? Endocr Pract. 2013;19(6):e158–62.
26. Hygum K, Wulff CN, Harsløf T, Boysen AK, Rossen PB, Langdahl BL, et al. Hypercalcemia in metastatic gist caused by systemic elevated calcitriol: a case report and review of the literature. BMC Cancer. 2015;15(1):1.
27. Tsikrikas S, Manolakopoulos S, Deutsch M, Alexakis G, Sialevris K, Giannopoulos D, et al. Unusual combination of paraneoplastic manifestations in a patient with metastatic gastrointestinal stromal tumor (gist). Scand J Gastroenterol. 2008;43(8):1012–5.
28. Maynard MA, Marino-Enriquez A, Fletcher JA, Dorfman DM, Raut CP, Yassa L, et al. Thyroid hormone inactivation in gastrointestinal stromal tumors. N Engl J Med. 2014;370(14):1327–34.
29. Pink D, Schoeler D, Lindner T, Thuss-Patience PC, Kretzschmar A, Knipp H, et al. Severe hypoglycemia caused by paraneo-

plastic production of igf-ii in patients with advanced gastrointestinal stromal tumors: a report of two cases. J Clin Oncol. 2005;23(27):6809–11.
30. Boikos SA, Pappo AS, Killian JK, LaQuaglia MP, Weldon CB, George S, et al. Molecular subtypes of kit/pdgfra wild-type gastrointestinal stromal tumors: a report from the national institutes of health gastrointestinal stromal tumor clinic. JAMA Oncol. 2016;2(7):922–8.
31. Burgoyne AM, Somaiah N, Sicklick JK. Gastrointestinal stromal tumors in the setting of multiple tumor syndromes. Curr Opin Oncol. 2014;26(4):408–14.
32. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol. 2005;100(1):162–8.
33. Cheung MC, Zhuge Y, Yang R, Koniaris LG. Disappearance of racial disparities in gastrointestinal stromal tumor outcomes. J Am Coll Surg. 2009;209(1):7–16.
34. Belloni M, De Fiori E, Mazzarol G, Curti A, Crosta C. Endoscopic ultrasound and computed tomography in gastric stromal tumours. La Radiologia Medica. 2001;103(1–2):65–73.
35. Chak A, Canto MI, Rösch T, Dittler HJ, Hawes RH, Tio TL, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. Gastrointest Endosc. 1997;45(6):468–73.
36. Palazzo L, Landi B, Cellier C, Cuillerier E, Roseau G, Barbier J. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. Gut. 2000;46(1):88–92.
37. Eriksson M, Reichardt P, Hall KS, Schütte J, Cameron S, Hohenberger P, et al. Needle biopsy through the abdominal wall for the diagnosis of gastrointestinal stromal tumour–does it increase the risk for tumour cell seeding and recurrence? Eur J Cancer. 2016;59:128–33.
38. (NCCN) NCCN. Nccn clinical practice guidelines in oncology. http://www.Nccn.Org/professionals/physician_gls/f_guidelines.Asp. Accessed 1 Nov 2015.
39. Kamiyama Y, Aihara R, Nakabayashi T, Mochiki E, Asao T, Kuwano H, et al. 18f-fluorodeoxyglucose positron emission tomography: useful technique for predicting malignant potential of gastrointestinal stromal tumors. World J Surg. 2005;29(11):1429–35.
40. Stroobants S, Goeminne J, Seegers M, Dimitrijevic S, Dupont P, Nuyts J, et al. 18 fdg-positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (glivec®). Eur J Cancer. 2003;39(14):2012–20.
41. Gayed I, Vu T, Iyer R, Johnson M, Macapinlac H, Swanston N, et al. The role of 18f-fdg pet in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. J NuclMed. 2004;45(1):17–21.
42. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279(5350):577–80.
43. Espinosa I, Lee C-H, Kim MK, Rouse B-T, Subramanian S, Montgomery K, et al. A novel monoclonal antibody against dog1 is a sensitive and specific marker for gastrointestinal stromal tumors. Am J Surg Pathol. 2008;32(2):210–8.
44. Lasota J, Miettinen M. Clinical significance of oncogenic kit and pdgfra mutations in gastrointestinal stromal tumours. Histopathology. 2008;53(3):245–66.
45. Lasota J, Jasinski M, Sarlomo-Rikala M, Miettinen M. Mutations in exon 11 of c-kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. Am J Pathol. 1999;154(1):53–60.
46. Lasota J, Corless CL, Heinrich MC, Debiec-Rychter M, Sciot R, Wardelmann E, et al. Clinicopathologic profile of gastrointestinal stromal tumors (gists) with primary kit exon 13 or exon 17 mutations: a multicenter study on 54 cases. Mod Pathol. 2008;21(4):476–84.
47. Hirota S, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y, et al. Gain-of-function mutations of platelet-derived growth factor receptor α gene in gastrointestinal stromal tumors. Gastroenterology. 2003;125(3):660–7.
48. Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen C-J, Joseph N, et al. Pdgfra activating mutations in gastrointestinal stromal tumors. Science. 2003;299(5607):708–10.
49. Italiano A, Chen C-L, Sung Y-S, Singer S, DeMatteo RP, LaQuaglia MP, et al. Sdha loss of function mutations in a subset of young adult wild-type gastrointestinal stromal tumors. BMC Cancer. 2012;12(1):1.
50. Oudijk L, Gaal J, Korpershoek E, van Nederveen FH, Kelly L, Schiavon G, et al. Sdha mutations in adult and pediatric wild-type gastrointestinal stromal tumors. Mod Pathol. 2013;26(3):456–63.
51. Pantaleo MA, Astolfi A, Urbini M, Nannini M, Paterini P, Indio V, et al. Analysis of all subunits, sdha, sdhb, sdhc, sdhd, of the succinate dehydrogenase complex in kit/pdgfra wild-type gist. Eur J Hum Genet. 2014;22(1):32–9.
52. Janeway KA, Kim SY, Lodish M, Nosé V, Rustin P, Gaal J, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking kit and pdgfra mutations. Proc Natl Acad Sci. 2011;108(1):314–8.
53. Miettinen M, Wang Z-F, Sarlomo-Rikala M, Osuch C, Rutkowski P, Lasota J. Succinate dehydrogenase deficient gists–a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric gists with predilection to young age. Am J Surg Pathol. 2011;35(11):1712.
54. Miettinen M, Lasota J. Succinate dehydrogenase deficient gastrointestinal stromal tumors (gists) – a review. Int J Biochem Cell Biol. 2014;53:514–9.
55. Janeway KA, Zhu MJ, Barretina J, Perez-Atayde A, Demetri GD, Fletcher JA. Strong expression of igf1r in pediatric gastrointestinal stromal tumors without igf1r genomic amplification. Int J Cancer. 2010;127(11):2718–22.
56. Agaimy A, Terracciano L, Dirnhofer S, Tornillo L, Foerster A, Hartmann A, et al. V600e braf mutations are alternative early molecular events in a subset of kit/pdgfra wild-type gastrointestinal stromal tumours. J Clin Pathol. 2009;62(7):613–6.
57. Agaram NP, Wong GC, Guo T, Maki RG, Singer S, DeMatteo RP, et al. Novel v600e braf mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. Genes Chromosom Cancer. 2008;47(10):853–9.
58. Nishida T, Hirota S, Taniguchi M, Hashimoto K, Isozaki K, Nakamura H, et al. Familial gastrointestinal stromal tumours with germline mutation of the kit gene. Nat Genet. 1998;19(4):323–4.
59. Neuhann TM, Mansmann V, Merkelbach-Bruse S, Klink B, Hellinger A, Höffkes H-G, et al. A novel germline kit mutation (p. L576p) in a family presenting with juvenile onset of multiple gastrointestinal stromal tumors, skin hyperpigmentations, and esophageal stenosis. Am J Surg Pathol. 2013;37(6):898–905.
60. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol. 2006;30(4):477–89.
61. Takazawa Y, Sakurai S, Sakuma Y, Ikeda T, Yamaguchi J, Hashizume Y, et al. Gastrointestinal stromal tumors of neurofibromatosis type i (von recklinghausen's disease). Am J Surg Pathol. 2005;29(6):755–63.
62. Maertens O, Prenen H, Debiec-Rychter M, Wozniak A, Sciot R, Pauwels P, et al. Molecular pathogenesis of multiple gastrointestinal stromal tumors in nf1 patients. Hum Mol Genet. 2006;15(6):1015–23.
63. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the carney triad. Am J Med Genet. 2002;108(2):132–9.

64. McWhinney SR, Pasini B, Stratakis CA. Familial gastrointestinal stromal tumors and germ-line mutations. N Engl J Med. 2007;357(10):1054–6.
65. Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, et al. Clinical and molecular genetics of patients with the carney–stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits sdhb, sdhc, and sdhd. Eur J Hum Genet. 2008;16(1):79–88.
66. Gaal J, Stratakis CA, Carney JA, Ball ER, Korpershoek E, Lodish MB, et al. Sdhb immunohistochemistry: a useful tool in the diagnosis of carney–stratakis and carney triad gastrointestinal stromal tumors. Mod Pathol. 2011;24(1):147–51.
67. Carney JA, Sheps SG, Go VL, Gordon H. The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med. 1977;296(26):1517–8.
68. Carney JA. Carney triad. Front Horm Res. 2013;41:92–110.
69. Matyakhina L, Bei TA, McWhinney SR, Pasini B, Cameron S, Gunawan B, et al. Genetics of carney triad: recurrent losses at chromosome 1 but lack of germline mutations in genes associated with paragangliomas and gastrointestinal stromal tumors. The Journal of Clinical Endocrinology & Metabolism. 2007;92(8):2938–43.
70. Stratakis C, Carney J. The triad of paragangliomas, gastric stromal tumours and pulmonary chondromas (carney triad), and the dyad of paragangliomas and gastric stromal sarcomas (carney–stratakis syndrome): molecular genetics and clinical implications. J Intern Med. 2009;266(1):43–52.
71. Pandurengan R, Dumont A, Araujo D, Ludwig J, Ravi V, Patel S, et al. Survival of patients with multiple primary malignancies: a study of 783 patients with gastrointestinal stromal tumor. Ann Oncol. 2010;21(10):2107–11:mdq078.
72. Agaimy A, Wünsch PH, Sobin LH, Lasota J, Miettinen M, editors. Occurrence of other malignancies in patients with gastrointestinal stromal tumors. Semin Diagn Pathol. 2006;23(2):120: Elsevier.
73. Miettinen M, Kraszewska E, Sobin LH, Lasota J. A nonrandom association between gastrointestinal stromal tumors and myeloid leukemia. Cancer. 2008;112(3):645–9.
74. Kosary CL, Ries LG, Miller B, Hankey B, Harras A, Edwards B. Seer cancer statistics review, 1973–1992: tables and graphs. Bethesda: National Cancer Institute; 1995:N1H.
75. Liu Y-J, Yang Z, Hao L-S, Xia L, Jia Q-B, Wu X-T. Synchronous incidental gastrointestinal stromal and epithelial malignant tumors. World J Gastroenterol. 2009;15(16):2027–31.
76. AbdullGaffar B. Gastrointestinal stromal tumors and extra-gastrointestinal tract neoplasms. South Med J. 2010;103(10):1004–8.
77. Dumont A, Rink L, Godwin A, Miettinen M, Joensuu H, Strosberg J, et al. A nonrandom association of gastrointestinal stromal tumor (gist) and desmoid tumor (deep fibromatosis): case series of 28 patients. Ann Oncol. 2011;23(5):1335–40:mdr442.
78. Huang H-Y, Li C-F, Huang W-W, Hu T-H, Lin C-N, Uen Y-H, et al. A modification of nih consensus criteria to better distinguish the highly lethal subset of primary localized gastrointestinal stromal tumors: a subdivision of the original high-risk group on the basis of outcome. Surgery. 2007;141(6):748–56.
79. Tryggvason G, Gíslason HG, Magnússon MK, Jónasson JG. Gastrointestinal stromal tumors in iceland, 1990–2003: the icelandic gist study, a population-based incidence and pathologic risk stratification study. Int J Cancer. 2005;117(2):289–93.
80. Nakamura N, Yamamoto H, Yao T, Oda Y, Nishiyama K-i, Imamura M, et al. Prognostic significance of expressions of cell-cycle regulatory proteins in gastrointestinal stromal tumor and the relevance of the risk grade. Hum Pathol. 2005;36(7):828–37.
81. Rutkowski P, Nowecki ZI, Michej W, D**ę**biec-Rychter M, Wo**ź**niak A, Limon J, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Ann Surg Oncol. 2007;14(7):2018–27.
82. Goh BK, Chow PK, Yap W-M, Kesavan SM, Song I-C, Paul PG, et al. Which is the optimal risk stratification system for surgically treated localized primary gist? comparison of three contemporary prognostic criteria in 171 tumors and a proposal for a modified armed forces institute of pathology risk criteria. Ann Surg Oncol. 2008;15(8):2153–63.
83. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. Am J Surg Pathol. 1999;23(1):82–7.
84. Bearzi I, Mandolesi A, Arduini F, Costagliola A, Ranaldi R. Gastrointestinal stromal tumor. A study of 158 cases: clinicopathological features and prognostic factors. Anal Quant Cytol Histol/Int Acad Cytol/Am Soc Cytol. 2006;28(3):137–47.
85. Miettinen M, Lasota J, Sobin LH. Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol. 2005;29(10):1373–81.
86. DeMatteo RP, Gold JS, Saran L, Gönen M, Liau KH, Maki RG, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (gist). Cancer. 2008;112(3):608–15.
87. Gold JS, Gönen M, Gutiérrez A, Broto JM, García-del-Muro X, Smyrk TC, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. The lancet oncology. 2009;10(11):1045–52.
88. Hohenberger P, Ronellenfitsch U, Oladeji O, Pink D, Ströbel P, Wardelmann E, et al. Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour. Br J Surg. 2010;97(12):1854–9.
89. Saponara M, Di Battista M, Lolli C, Derenzini E, Pantaleo M, Santini D, et al., editors. Evaluation of ki-67 in gastrointestinal stromal tumor (gist). In: ASCO annual meeting proceedings; 2009.
90. Wang YM, Gu ML, Ji F. Succinate dehydrogenase-deficient gastrointestinal stromal tumors. World J Gastroenterol. 2015;21(8):2303–14.
91. Kim TW, Lee H, Kang Y-K, Choe MS, Ryu M-H, Chang HM, et al. Prognostic significance of c-kit mutation in localized gastrointestinal stromal tumors. Clin Cancer Res. 2004;10(9):3076–81.
92. Singer S, Rubin BP, Lux ML, Chen C-J, Demetri GD, Fletcher CD, et al. Prognostic value of kit mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. J Clin Oncol. 2002;20(18):3898–905.
93. Corless CL, McGreevey L, Haley A, Town A, Heinrich MC. Kit mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. Am J Pathol. 2002;160(5):1567–72.
94. Andersson J, Bümming P, Meis-Kindblom JM, Sihto H, Nupponen N, Joensuu H, et al. Gastrointestinal stromal tumors with kit exon 11 deletions are associated with poor prognosis. Gastroenterology. 2006;130(6):1573–81.
95. Rubin BP, Singer S, Tsao C, Duensing A, Lux ML, Ruiz R, et al. Kit activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res. 2001;61(22):8118–21.
96. Martín J, Poveda A, Llombart-Bosch A, Ramos R, López-Guerrero JA, del Muro JG, et al. Deletions affecting codons 557-558 of the c-kit gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the spanish group for sarcoma research (geis). J Clin Oncol. 2005;23(25):6190–8.
97. Lasota J, Dansonka-Mieszkowska A, Stachura T, Schneider-Stock R, Kallajoki M, Steigen SE, et al. Gastrointestinal stromal tumors with internal tandem duplications in 3′ end of kit juxtamembrane

domain occur predominantly in stomach and generally seem to have a favorable course. Mod Pathol. 2003;16(12):1257–64.
98. Lasota J, Dansonka-Mieszkowska A, Sobin LH, Miettinen M. A great majority of gists with pdgfra mutations represent gastric tumors of low or no malignant potential. Lab Investig. 2004;84(7):874–83.
99. Lasota J, Stachura J, Miettinen M. Gists with pdgfra exon 14 mutations represent subset of clinically favorable gastric tumors with epithelioid morphology. Lab Investig. 2006;86(1):94–100.
100. Heinrich MC, Corless CL. Gastric gi stromal tumors (gists): the role of surgery in the era of targeted therapy. J Surg Oncol. 2005;90(3):195–207.
101. Agaimy A, Wünsch PH, Hofstaedter F, Blaszyk H, Rümmele P, Gaumann A, et al. Minute gastric sclerosing stromal tumors (gist tumorlets) are common in adults and frequently show c-kit mutations. Am J Surg Pathol. 2007;31(1):113–20.
102. Kawanowa K, Sakuma Y, Sakurai S, Hishima T, Iwasaki Y, Saito K, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol. 2006;37(12):1527–35.
103. Davila RE, Faigel DO. Gi stromal tumors. Gastrointest Endosc. 2003;58(1):80–8.
104. Novitsky YW, Kercher KW, Sing RF, Heniford BT. Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. Ann Surg. 2006;243(6):738–47.
105. Otani Y, Furukawa T, Yoshida M, Saikawa Y, Wada N, Ueda M, et al. Operative indications for relatively small (2–5 cm) gastrointestinal stromal tumor of the stomach based on analysis of 60 operated cases. Surgery. 2006;139(4):484–92.
106. Bischof DA, Kim Y, Dodson R, Jimenez MC, Behman R, Cocieru A, et al. Open versus minimally invasive resection of gastric gist: a multi-institutional analysis of short-and long-term outcomes. Ann Surg Oncol. 2014;21(9):2941–8.
107. Pelletier J-S, Gill RS, Gazala S, Karmali S. A systematic review and meta-analysis of open vs. Laparoscopic resection of gastric gastrointestinal stromal tumors. J Clin Med Res. 2015;7(5):289.
108. Fujimoto Y, Nakanishi Y, Yoshimura K, Shimoda T. Clinicopathologic study of primary malignant gastrointestinal stromal tumor of the stomach, with special reference to prognostic factors: analysis of results in 140 surgically resected patients. Gastric Cancer. 2003;6(1):0039–48.
109. Duffaud F, Meeus P, Bachet J, Cassier P, Huynh T, Boucher E, et al. Conservative surgery vs. duodeneopancreatectomy in primary duodenal gastrointestinal stromal tumors (gist): a retrospective review of 114 patients from the french sarcoma group (fsg). Eur J Surg Oncol. 2014;40(10):1369–75.
110. Colombo C, Ronellenfitsch U, Yuxin Z, Rutkowski P, Miceli R, Bylina E, et al. Clinical, pathological and surgical characteristics of duodenal gastrointestinal stromal tumor and their influence on survival: a multi-center study. Ann Surg Oncol. 2012;19(11):3361–7.
111. Clary BM, DeMatteo RP, Lewis JJ, Leung D, Brennan MF. Gastrointestinal stromal tumors and leiomyosarcoma of the abdomen and retroperitoneum: a clinical comparison. Ann Surg Oncol. 2001;8(4):290–9.
112. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg. 2000;231(1):51.
113. Pierie J-PE, Choudry U, Muzikansky A, Yeap BY, Souba WW, Ott MJ. The effect of surgery and grade on outcome of gastrointestinal stromal tumors. Arch Surg. 2001;136(4):383–9.
114. Raut CP, Espat NJ, Maki RG, Araujo DM, Keir CH, Williams TF, et al., editors. Adjuvant imatinib (im) for patients (pts) with primary gastrointestinal stromal tumor (gist) at significant risk of recurrence: persist-5 planned 3-year interim analysis. In: ASCO annual meeting proceedings; 2015.
115. DeMatteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373(9669):1097–104.
116. Joensuu H, Eriksson M, Hall KS, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA. 2012;307(12):1265–72.
117. DeMatteo R, Owzar K, Antonescu C, Maki R, Demetri G, McCarter M, et al., editors. Efficacy of adjuvant imatinib mesylate following complete resection of localized, primary gastrointestinal stromal tumor (gist) at high risk of recurrence: the us intergroup phase ii trial acosog z9000. In: Gastrointestinal cancers symposium; 2008.
118. Casali PG, Le Cesne A, Poveda Velasco A, Kotasek D, Rutkowski P, Hohenberger P, et al., editors. Imatinib failure-free survival (ifs) in patients with localized gastrointestinal stromal tumors (gist) treated with adjuvant imatinib (im): the eortc/agitg/fsg/geis/isg randomized controlled phase iii trial. In: ASCO annual meeting proceedings; 2013.
119. DeMatteo RP, Ballman KV, Antonescu CR, Corless C, Kolesnikova V, Von Mehren M, et al. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor (gist): acosog z9000 (alliance) intergroup phase 2 trial. Ann Surg. 2013;258(3):422.
120. Corless CL, Ballman KV, Antonescu CR, Kolesnikova V, Maki RG, Pisters PW, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary gi stromal tumor: the acosog z9001 trial. J Clin Oncol. 2014;32(15):1563–70.
121. Blesius A, Cassier PA, Bertucci F, Fayette J, Ray-Coquard I, Bui B, et al. Neoadjuvant imatinib in patients with locally advanced non metastatic gist in the prospective bfr14 trial. BMC Cancer. 2011;11(1):1.
122. Sjölund K, Andersson A, Nilsson E, Nilsson O, Ahlman H, Nilsson B. Downsizing treatment with tyrosine kinase inhibitors in patients with advanced gastrointestinal stromal tumors improved resectability. World J Surg. 2010;34(9):2090–7.
123. Eisenberg BL, Harris J, Blanke CD, Demetri GD, Heinrich MC, Watson JC, et al. Phase ii trial of neoadjuvant/adjuvant imatinib mesylate (im) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (gist): early results of rtog 0132/acrin 6665. J Surg Oncol. 2009;99(1):42–7.
124. Wang D, Zhang Q, Blanke CD, Demetri GD, Heinrich MC, Watson JC, et al. Phase ii trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of radiation therapy oncology group 0132. Ann Surg Oncol. 2012;19(4):1074–80.
125. Rutkowski P, Gronchi A, Hohenberger P, Bonvalot S, Schöffski P, Bauer S, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (gist): the eortc stbsg experience. Ann Surg Oncol. 2013;20(9):2937–43.
126. DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg. 2007;245(3):347–52.
127. Blanke CD, Demetri GD, Von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, et al. Long-term results from a randomized phase ii trial of standard-versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing kit. J Clin Oncol. 2008;26(4):620–5.
128. van Oosterom AT, Judson IR, Verweij J, Stroobants S, Dumez H, Donato di Paola E, et al. Update of phase i study of imatinib (sti571) in advanced soft tissue sarcomas and gastrointestinal stromal

tumors: a report of the eortc soft tissue and bone sarcoma group. Eur J Cancer (Oxford, England: 1990). 2002;38(Suppl 5):S83–7.
129. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347(7):472–80.
130. Verweij J, van Oosterom A, Blay J-Y, Judson I, Rodenhuis S, van der Graaf W, et al. Imatinib mesylate (sti-571 glivec®, gleevec™) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target: Results from an eortc soft tissue and bone sarcoma group phase ii study. Eur J Cancer. 2003;39(14):2006–11.
131. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay J-Y, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet. 2004;364(9440):1127–34.
132. Blanke CD, Rankin C, Demetri GD, Ryan CW, Von Mehren M, Benjamin RS, et al. Phase iii randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol. 2008;26(4):626–32.
133. Blay J-Y, Le Cesne A, Ray-Coquard I, Bui B, Duffaud F, Delbaldo C, et al. Prospective multicentric randomized phase iii study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the french sarcoma group. J Clin Oncol. 2007;25(9):1107–13.
134. Von Mehren M, Heinrich M, Joensuu H, Blanke C, Wehrle E, Demetri G, editors. Follow-up results after 9 years (yrs) of the ongoing, phase ii b2222 trial of imatinib mesylate (im) in patients (pts) with metastatic or unresectable kit+ gastrointestinal stromal tumors (gist). In: ASCO annual meeting proceedings; 2011.
135. Zalcberg JR, Verweij J, Casali PG, Le Cesne A, Reichardt P, Blay J-Y, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800mg after progression on 400mg. Eur J Cancer. 2005;41(12):1751–7.
136. Group GSTM-A. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol. 2010;28(7):1247–53.
137. Patrikidou A, Chabaud S, Ray-Coquard I, Bui B, Adenis A, Rios M, et al. Influence of imatinib interruption and rechallenge on the residual disease in patients with advanced gist: results of the bfr14 prospective french sarcoma group randomised, phase iii trial. Ann Oncol. 2013;24(4):1087–93.
138. Trent JC, Patel SS, Zhang J, Araujo DM, Plana JC, Lenihan DJ, et al. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. Cancer. 2010;116(1):184–92.
139. Khakoo A, Steinert D, Patel S, Plana J, Ludwig J, Benjamin R, et al., editors. Rare incidence of congestive heart failure (chf) in gastrointestinal stromal tumor (gist) and other sarcoma patients (pts) receiving imatinib mesylate (im) therapy. In: ASCO annual meeting proceedings; 2007.
140. Heinrich MC, Corless CL, Demetri GD, Blanke CD, Von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21(23):4342–9.
141. Cassier PA, Fumagalli E, Rutkowski P, Schöffski P, Van Glabbeke M, Debiec-Rychter M, et al. Outcome of patients with platelet-derived growth factor receptor alpha–mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Clin Cancer Res. 2012;18(16):4458–64.
142. Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, et al. Pdgfra mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol. 2005;23(23):5357–64.
143. McAuliffe JC, Hunt KK, Lazar AJ, Choi H, Qiao W, Thall P, et al. A randomized, phase ii study of preoperative plus postoperative imatinib in gist: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. Ann Surg Oncol. 2009;16(4):910–9.
144. Bechtold R, Chen M, Stanton C, Savage P, Levine E. Cystic changes in hepatic and peritoneal metastases from gastrointestinal stromal tumors treated with gleevec. Abdom Imaging. 2003;28(6):808–14.
145. Linton KM, Taylor M, Radford JA. Response evaluation in gastrointestinal stromal tumours treated with imatinib: misdiagnosis of disease progression on ct due to cystic change in liver metastases. Br J Radiol. 2014;79(944):e40–4.
146. Van den Abbeele AD. The lessons of gist—pet and pet/ct: a new paradigm for imaging. Oncologist. 2008;13(Supplement 2):8–13.
147. Benjamin RS, Choi H, Macapinlac HA, Burgess MA, Patel SR, Chen LL, et al. We should desist using recist, at least in gist. J Clin Oncol. 2007;25(13):1760–4.
148. Desai J, Shankar S, Heinrich MC, Fletcher JA, Fletcher CD, Manola J, et al. Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. Clin Cancer Res. 2007;13(18):5398–405.
149. Andtbacka RH, Ng CS, Scaife CL, Cormier JN, Hunt KK, Pisters PW, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol. 2007;14(1):14–24.
150. Raut CP, Posner M, Desai J, Morgan JA, George S, Zahrieh D, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol. 2006;24(15):2325–31.
151. Bonvalot S, Eldweny H, Le Pechoux C, Vanel D, Terrier P, Cavalcanti A, et al. Impact of surgery on advanced gastrointestinal stromal tumors (gist) in the imatinib era. Ann Surg Oncol. 2006;13(12):1596–603.
152. Rutkowski P, Nowecki Z, Nyckowski P, Dziewirski W, Grzesiakowska U, Nasierowska-Guttmejer A, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (gist) during therapy with imatinib mesylate. J Surg Oncol. 2006;93(4):304–11.
153. Al-Batran S-E, Hartmann JT, Heidel F, Stoehlmacher J, Wardelmann E, Dechow C, et al. Focal progression in patients with gastrointestinal stromal tumors after initial response to imatinib mesylate: a three-center-based study of 38 patients. Gastric Cancer. 2007;10(3):145–52.
154. Mussi C, Ronellenfitsch U, Jakob J, Tamborini E, Reichardt P, Casali P, et al. Post-imatinib surgery in advanced/metastatic gist: is it worthwhile in all patients? Ann Oncol. 2010;21(2):403–8.
155. Park SJ, Ryu MH, Ryoo BY, Park YS, Sohn BS, Kim HJ, et al. The role of surgical resection following imatinib treatment in patients with recurrent or metastatic gastrointestinal stromal tumors: results of propensity score analyses. Ann Surg Oncol. 2014;21(13):4211–7.
156. Rubió-Casadevall J, Martinez-Trufero J, Garcia-Albeniz X, Calabuig S, Lopez-Pousa A, del Muro JG, et al. Role of surgery in patients with recurrent, metastatic, or unresectable locally advanced gastrointestinal stromal tumors sensitive to imatinib: a retrospective analysis of the spanish group for research on sarcoma (geis). Ann Surg Oncol. 2015;22(9):2948–57.
157. Zalinski S, Palavecino M, Abdalla EK. Hepatic resection for gastrointestinal stromal tumor liver metastases. Hematol Oncol Clin North Am. 2009;23(1):115–27.
158. Vassos N, Agaimy A, Hohenberger W, Croner RS. Management of liver metastases of gastrointestinal stromal tumors (gist). Ann Hepatol. 2015;14(4):531–9.

159. Maluccio MA, Covey AM, Schubert J, Brody LA, Sofocleous CT, Getrajdman GI, et al. Treatment of metastatic sarcoma to the liver with bland embolization. Cancer. 2006;107(7):1617–23.
160. Kobayashi K, Gupta S, Trent JC, Vauthey JN, Krishnamurthy S, Ensor J, et al. Hepatic artery chemoembolization for 110 gastrointestinal stromal tumors. Cancer. 2006;107(12):2833–41.
161. Kobayashi K, Szklaruk J, Trent JC, Ensor J, Ahrar K, Wallace MJ, et al. Hepatic arterial embolization and chemoembolization for imatinib-resistant gastrointestinal stromal tumors. Am J Clin Oncol. 2009;32(6):574–81.
162. Heinrich MC, Owzar K, Corless CL, Hollis D, Borden EC, Fletcher CD, et al. Correlation of kinase genotype and clinical outcome in the north american intergroup phase iii trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: Calgb 150105 study by cancer and leukemia group b and southwest oncology group. J Clin Oncol. 2008;26(33):5360–7.
163. Heinrich MC, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol. 2008;26(33):5352–9.
164. Eechoute K, Sparreboom A, Burger H, Franke RM, Schiavon G, Verweij J, et al. Drug transporters and imatinib treatment: implications for clinical practice. Clin Cancer Res. 2011;17(3):406–15.
165. Antonescu CR, Besmer P, Guo T, Arkun K, Hom G, Koryotowski B, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res. 2005;11(11):4182–90.
166. Wardelmann E, Merkelbach-Bruse S, Pauls K, Thomas N, Schildhaus H-U, Heinicke T, et al. Polyclonal evolution of multiple secondary kit mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. Clin Cancer Res. 2006;12(6):1743–9.
167. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329–38.
168. Demetri GD, Garrett CR, Schöffski P, Shah MH, Verweij J, Leyvraz S, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase iii trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res. 2012;18(11):3170–9.
169. Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med. 2006;145(9):660–4.
170. Kindler H, Campbell N, Wroblewski K, Maki R, D'Adamo D, Chow W, et al., editors. Sorafenib (sor) in patients (pts) with imatinib (im) and sunitinib (su)-resistant (res) gastrointestinal stromal tumors (gist): final results of a university of chicago phase ii consortium trial. In: ASCO annual meeting proceedings; 2011.
171. Park S, Ryu M, Ryoo B, Im S, Kwon H, Lee S, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase ii study of korean gastrointestinal stromal tumors study group. Investig New Drugs. 2012;30(6):2377–83.
172. Reichardt P, Blay J-Y, Gelderblom H, Schlemmer M, Demetri G, Bui-Nguyen B, et al. Phase iii study of nilotinib versus best supportive care with or without a tki in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol. 2012;23(7):1680–7.
173. Montemurro M, Schöffski P, Reichardt P, Gelderblom H, Schütte J, Hartmann J, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer. 2009;45(13):2293–7.
174. Dewaele B, Wasag B, Cools J, Sciot R, Prenen H, Vandenberghe P, et al. Activity of dasatinib, a dual src/abl kinase inhibitor, and ipi-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor–associated pdgfrad842v mutation. Clin Cancer Res. 2008;14(18):5749–58.
175. Trent J, Wathen K, Von Mehren M, Samuels B, Staddon A, Choy E, et al., editors. A phase ii study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (gist). In: ASCO annual meeting proceedings; 2011.
176. Le Cesne A, Blay J-Y, Bui BN, Bouché O, Adenis A, Domont J, et al. Phase ii study of oral masitinib mesilate in imatinib-naive patients with locally advanced or metastatic gastro-intestinal stromal tumour (gist). Eur J Cancer. 2010;46(8):1344–51.
177. Blay J, Le Cesne A, Bin Bui N, Bouché O, Adenis A, Julien D, et al., editors. Overall survival benefit with masitinib mesylate in imatinib-naive, locally advanced, or metastatic gastrointestinal stromal tumor (gist): 4-years follow-up of the french sarcoma group phase ii trial. In: ASCO annual meeting proceedings; 2011.
178. Ganjoo KN, Villalobos V, Kamaya A, Fisher G, Butrynski J, Morgan J, et al. A multicenter phase ii study of pazopanib in patients with advanced gastrointestinal stromal tumors (gist) following failure of at least imatinib and sunitinib. Ann Oncol. 2014;25(1):236–40.
179. Heinrich MC, von Mehren M, Demetri GD, Fletcher JA, Sun J, Hodgson JG, et al., editors. A phase 2 study of ponatinib in patients (pts) with advanced gastrointestinal stromal tumors (gist) after failure of tyrosine kinase inhibitor (tki) therapy: initial report. In: ASCO annual meeting proceedings; 2014.
180. George S, Wang Q, Heinrich MC, Corless CL, Zhu M, Butrynski JE, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable gi stromal tumor after failure of imatinib and sunitinib: a multicenter phase ii trial. J Clin Oncol. 2012;30(19):2401–7. https://doi.org/10.1200/JCO.2011.39.9394.
181. Demetri GD, Reichardt P, Kang Y-K, Blay J-Y, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (grid): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295–302.
182. Van den Abbeele A, Badawi R, Manola J, Morgan J, Desai J, Kazanovicz A, et al., editors. Effects of cessation of imatinib mesylate (im) therapy in patients (pts) with im-refractory gastrointestinal stromal tumors (gist) as visualized by fdg-pet scanning. In: ASCO annual meeting proceedings; 2004.
183. Fumagalli E, Coco P, Morosi C, editors. Rechallenge with imatinib in gist patients resistant to second or third line therapy. In: 15th annual CTOS meeting; 2009.
184. Kang Y-K, Ryu M-H, Yoo C, Ryoo B-Y, Kim HJ, Lee JJ, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (right): a randomised, placebo-controlled, phase 3 trial. The lancet oncology. 2013;14(12):1175–82.
185. Demetri GD, Casali PG, Blay J-Y, von Mehren M, Morgan JA, Bertulli R, et al. A phase i study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res. 2009;15(18):5910–6.
186. Cauchi C, Somaiah N, Engstrom P, Litwin S, Lopez M, Lee J, et al. Evaluation of nilotinib in advanced gist previously treated with imatinib and sunitinib. Cancer Chemother Pharmacol. 2012;69(4):977–82.
187. Sawaki A, Nishida T, Yamada Y, Komatsu Y, Kanda T, Kakeji Y, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer. 2011;117(20):4633–41.
188. Blay J-Y, Shen L, Kang Y-K, Rutkowski P, Qin S, Nosov D, et al., editors. Phase iii trial of nilotinib versus imatinib as first-line targeted therapy of advanced gastrointestinal stromal tumors (gist). In: ASCO annual meeting proceedings; 2013.
189. Montemurro M, Gelderblom H, Bitz U, Schütte J, Blay J, Joensuu H, et al. Sorafenib as third-or fourth-line treatment of advanced

gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: a retrospective analysis. Eur J Cancer. 2013;49(5):1027–31.
190. Adenis A, Blay J-Y, Bui-Nguyen B, Bouché O, Bertucci F, Isambert N, et al. Masitinib in advanced gastrointestinal stromal tumor (gist) after failure of imatinib: a randomized controlled open-label trial. Ann Oncol. 2014;25(9):1762–9.
191. Joensuu H, De Braud F, Grignagni G, De Pas T, Spitalieri G, Coco P, et al. Vatalanib for metastatic gastrointestinal stromal tumour (gist) resistant to imatinib: final results of a phase ii study. Br J Cancer. 2011;104(11):1686–90.
192. Garner AP, Gozgit JM, Anjum R, Vodala S, Schrock A, Zhou T, et al. Ponatinib inhibits polyclonal drug-resistant kit oncoproteins and shows therapeutic potential in heavily pretreated gastrointestinal stromal tumor (gist) patients. Clin Cancer Res. 2014;20(22):5745–55.
193. Heinrich MC, Griffith D, McKinley A, Patterson J, Presnell A, Ramachandran A, et al. Crenolanib inhibits the drug-resistant pdgfra d842v mutation associated with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res. 2012;18(16):4375–84.
194. Falkenhorst J, Hamacher R, Bauer S. New therapeutic agents in gastrointestinal stromal tumours. Curr Opin Oncol. 2019; https://doi.org/10.1097/CCO.0000000000000549. [Epub ahead of print] PubMed PMID: 31033566.
195. Doebele RC, Davis LE, Vaishnavi A, Le AT, Estrada-Bernal A, Keysar S, et al. An oncogenic ntrk fusion in a patient with soft-tissue sarcoma with response to the tropomyosin-related kinase inhibitor loxo-101. Cancer discovery. 2015;5(10):1049–57.
196. Tarn C, Rink L, Merkel E, Flieder D, Pathak H, Koumbi D, et al. Insulin-like growth factor 1 receptor is a potential therapeutic target for gastrointestinal stromal tumors. Proc Natl Acad Sci. 2008;105(24):8387–92.
197. Dickson M, Okuno SH, Keohan M, Maki R, D'adamo D, Akhurst T, et al. Phase ii study of the hsp90-inhibitor biib021 in gastrointestinal stromal tumors. Ann Oncol. 2013;24(1):252–7.
198. Bauer S, Hilger R, Mühlenberg T, Grabellus F, Nagarajah J, Hoiczyk M, et al. Phase i study of panobinostat and imatinib in patients with treatment-refractory metastatic gastrointestinal stromal tumors. Br J Cancer. 2014;110(5):1155–62.
199. Van Oosterom A, Dumez H, Desai J, Stroobants S, Van Den Abbeele A, Clement P, et al., editors. Combination signal transduction inhibition: a phase i/ii trial of the oral mtor-inhibitor everolimus (e, rad001) and imatinib mesylate (im) in patients (pts) with gastrointestinal stromal tumor (gist) refractory to im. In: ASCO annual meeting proceedings; 2004.
200. Chi P, Chen Y, Zhang L, Guo X, Wongvipat J, Shamu T, et al. Etv1 is a lineage-specific survival factor in gist and cooperates with kit in oncogenesis. Nature. 2010;467(7317):849.
201. Floris G, Wozniak A, Sciot R, Li H, Friedman L, Van Looy T, et al. A potent combination of the novel pi3k inhibitor, gdc-0941, with imatinib in gastrointestinal stromal tumor xenografts: long-lasting responses after treatment withdrawal. Clin Cancer Res. 2013;19(3):620–30.
202. Chen LL, Chen X, Choi H, Sang H, Chen LC, Zhang H, et al. Exploiting antitumor immunity to overcome relapse and improve remission duration. Cancer Immunol Immunother. 2012;61(7):1113–24.
203. D'Angelo SP, Shoushtari AN, Keohan ML, Dickson MA, Gounder MM, Chi P, et al. Combined kit and ctla-4 blockade in patients with refractory gist and other advanced sarcomas: a phase ib study of dasatinib plus ipilimumab. Clin Cancer Res. 2016;23(12):2972–80.

Gastrointestinal Cancers in Children

18

M. Tezer Kutluk and Erman Ataş

Introduction

The incidence of pediatric cancers has been increasing since the 1970s [1]. Leukemia, central nervous system (CNS) tumors, and lymphomas are the most common cancer types in children [1, 2]. However, gastrointestinal (GI) cancers are very rare in childhood (see Table 18.1) [3–12]. They all represent less than 5% of pediatric neoplasm [13], but the true incidence is not well known because of the rarity of these tumors and different referral patterns. The rate of alimentary tract malignancies in children is reported to be as low as 1.2% by a recent study [14]. Primary gastrointestinal lymphoma is the most common GI malignancy [14, 15]. The frequency of hepatic tumors among childhood malignancies is 0.6–1.5% [1, 2]. Others including stomach, pancreas, colorectal, carcinoid, and gastrointestinal stromal tumors have a lower incidence rates. This chapter aims to provide an overview of the liver and gastrointestinal tract malignancies in children.

Malignancies of Liver

Hepatic tumors can be classified as benign or malignant. Two-thirds of these are malignant. Benign and malignant neoplasms of the liver are summarized in Table 18.2. Hepatic tumors are very rare in children with the rate of 0.6–1.5% [1, 2, 16]. For example, hepatic malign tumors constitute 1.4% of all childhood cancers in Turkey [2]. Approximately 65–90% of primary liver tumors constitute hepatoblastoma and hepatocellular carcinomas [2, 17–19].

Table 18.1 Gastrointestinal cancers in children

Origin		
Lymphoid	Incidence/cases per million	References
Primary gastrointestinal lymphoma	1.9	[6]
Blastemal		
Hepatoblastoma	0.8–1.6	[3]
Mesenchymal		
GIST	0.02–0.08	[11, 12]
Epithelial		
Colorectal carcinoma	0.2–1	[8, 9]
Hepatocellular carcinoma	0.29–0.45	[4, 5]
Esophageal cancer	Case-based	
Gastric cancer	Case-based	
Pancreatic cancers	0.46	[7]
Neuroendocrine		
Carcinoid tumor	1	[10]

GIST gastrointestinal stroma sarcoma

Table 18.2 Benign and malignant neoplasms of the liver

Benign neoplasms
Hepatic hemangiomas
Mesenchymal hamartomas
Focal nodular hyperplasia
Hepatic adenomas
Malignant neoplasms
More common
Hepatoblastoma
Hepatocellular carcinoma
Metastatic tumors of the liver (neuroblastoma, Wilm's tumor, lymphoma)
Less common
Undifferentiated embryonal sarcoma
Infantile choriocarcinoma of the liver
Epithelioid hemangioendothelioma
Embryonal rhabdomyosarcoma of the biliary system

M. T. Kutluk (✉)
Department of Pediatrics, Division of Pediatric Oncology, Hacettepe University Faculty of Medicine & Cancer Institute, Hacettepe University Oncology Hospital, Yenişehir, Ankara, Turkey

E. Ataş
Department of Pediatrics, Division of Pediatric Oncology, University of Health Sciences, Gulhane Training and Research Hospital, Etlik/Kecioren, Ankara, Turkey

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_18

Blastemal Origin

Hepatoblastoma

Epidemiology

Hepatoblastoma makes up 1% of pediatric malignancies. The incidence is 0.5–1.5 cases per million children younger than 15 years of age in developed countries [20]. It is the most common primary malignant tumor of the liver (43–75%). The mean age is 3.2 ± 0.8 years (90% of primary liver tumors under 3 years) [4, 21]. The male-to-female incidence ratio is 1.7:1. There is an association with increased survival of very-low-birth-weight premature infants [22]. Most cases are sporadic, but loss of heterozygosity at 11p15.5, trisomy 20, 2, 18, Beckwith-Wiedemann syndrome, Gardner's syndrome, familial adenomatous polyposis, adrenal agenesis, and hemihypertrophy are associated conditions [2, 17–19].

Pathology

The histopathological subgroups are epithelial (fetal, embryonal, small-cell undifferentiated, and anaplastic) and mixed epithelial/mesenchymal types [23]. Biphasic pattern (fetal and embryonal epithelial cells) is pathognomonic for hepatoblastoma. This is helpful to distinguish hepatoblastoma from hepatocellular carcinoma.

Clinical Presentation

Palpable nontender abdominal mass, enlarging abdomen, abdominal pain, anorexia, loss of weight, nausea, vomiting, and jaundice are the major clinical symptoms and findings. The right lobe is involved in nearly 60% and both lobes are involved in one-third of patients [23–25].

Diagnosis

In addition to history and physical examination, radiological investigations and alpha-fetoprotein (AFP) levels are essential in diagnosis before taking a biopsy. AFP levels are elevated in 90% of the cases [26] and correlate with tumor size and presence of metastases. It is also helpful to monitor the recurrence. Radiographic investigations including ultrasonography, abdominal computed tomography (CT), and magnetic resonance (MR) [27] are helpful to show the hepatic mass and dissemination of the disease inside the liver and abdomen. Thorax CT is necessary to investigate the pulmonary metastasis that may be seen in about 20% at the time of diagnosis [28]. Image-guided Tru-cut biopsy is required to make a final diagnosis.

Prognostic Factors

Very low birth weight, extreme prematurity and normal AFP levels, small-cell undifferentiated histology, loss of heterozygosity 11p15.5, and high human telomerase reverse transcriptase levels are poor prognosis factors [26, 29–31].

Staging

There are two staging system in childhood hepatoblastoma. The Children's Oncology Group (COG) uses a postoperative staging system (see Table 18.3) [32]. Risk groups stratified after surgery are shown in Table 18.4 [33].

The International Childhood Liver Tumor Strategy Group within the International Society of Pediatric Oncology Group has developed the SIOPEL PRETEXT (pretreatment extent of disease) staging system (Table 18.5 [34, 35]; Fig. 18.1 [36]) [32, 35]. Finally, risk groups according to COG are combined with PRETEXT (see Table 18.6) [35]. According to SIOPEL, standard, high, and very high-risk groups are shown in Table 18.7 [34, 35, 37–41].

Treatment

Complete surgical resection is essential for the cure of disease. Complete surgical resection at presentation is possible in less than 50% of the cases, and only 50% of patients with completely resected tumors survived before effective chemotherapy. A 1-cm safe resection margin is considered essential. However, a 1-cm safe margin may not always be possible when resecting a large mass that compresses vascular structures. In patients with microscopic residual disease after neoadjuvant chemotherapy and surgery, postsurgical chemotherapy may

Table 18.3 Postoperative staging system [32]

Stage I	Complete resection of tumor, no metastasis
Stage II	Microscopic residual tumor (positive margin, tumor rupture, tumor spill at surgery), no metastasis
Stage III	Unresectable or macroscopic residual tumor or lymph node involvement, no distant metastasis
Stage IV	Distant metastases (lung)

Table 18.4 Risk groups stratification of hepatoblastoma after surgery [33]

Risk group	Definition	Treatment
Very low	Stage I with pure PFH	Surgery alone
Low	Stage I with non-PFH, non-SCU, or stage II with non-SCU	Two courses of adjuvant cisplatin, 5-flourouracil, and vincristine
Intermediate	Stage I with SCU, stage II with SCU, or stage III	Cisplatin, 5-flourouracil, and vincristine plus doxorubicin
High	Stage IV or any stage plus initial AFP <100 ng/ml	Irinotecan is being investigated

AFP alpha-fetoprotein, *PFH* pure fetal histology, *SCU* small-cell undifferentiated type

Table 18.5 SIOPEL PRETEXT staging system [34, 35]

PRETEXT I	One sector, three adjoining sectors free
PRETEXT II	Two sectors involved, two sectors free
PRETEXT III	Three sectors involved, no adjoining sectors free
PRETEXT IV	All four sectors involved

SIOPEL Société Internationale d'Oncologie Pédiatrique – Epithelial Liver, *PRETEXT* pretreatment extent of disease

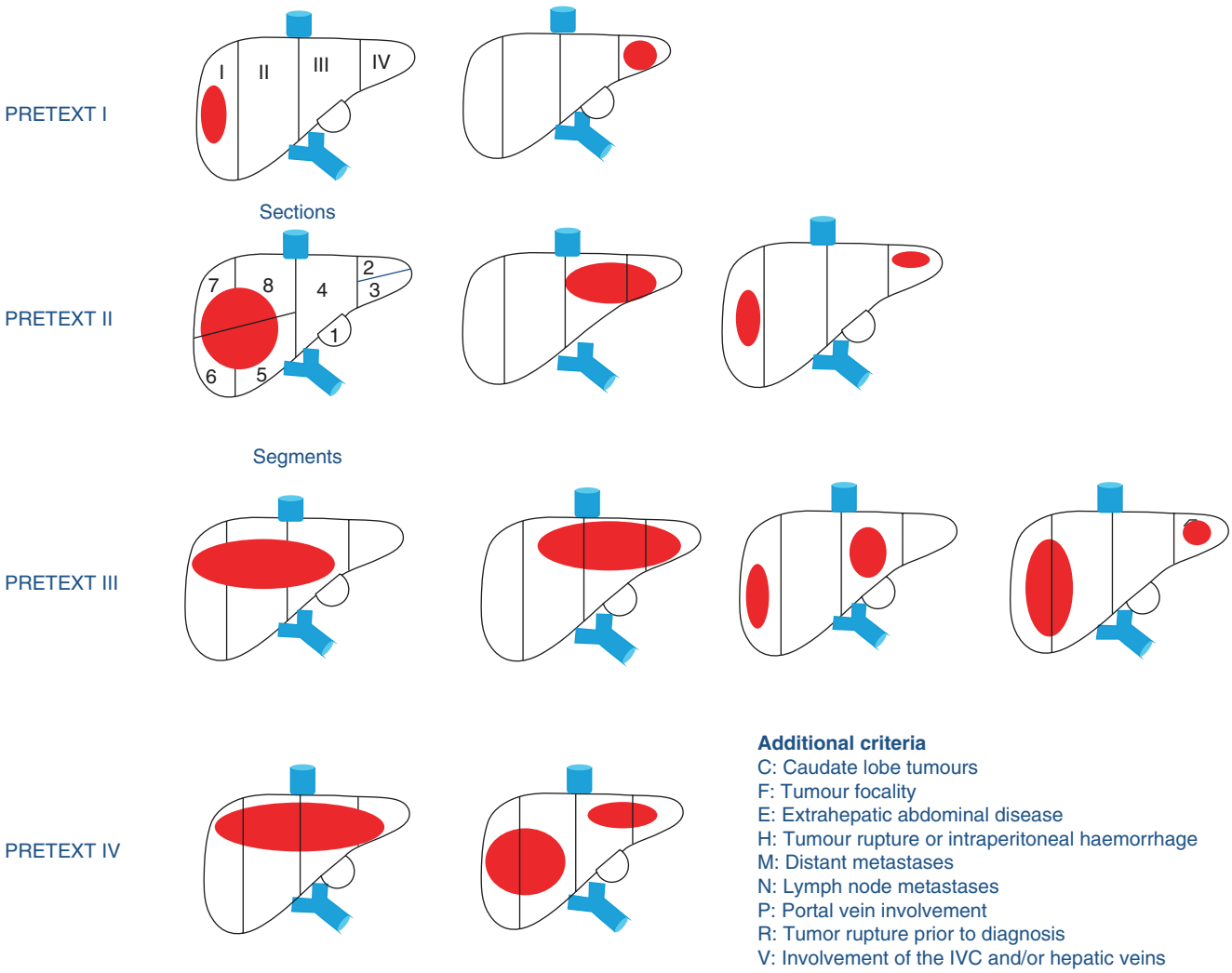


Fig. 18.1 PRETEXT (pretreatment extent of disease) classification system with additional criteria [36]

Table 18.6 Combination of Children's Oncology Group (COG) risk groups with PRETEXT [35]

Risk group	Definition
Very low	PRETEXT I or II with PFH and primary resection at diagnosis
Low	PRETEXT I or II of any histology with primary resection at diagnosis
Intermediate	PRETEXT II, III, and IV unresectable at diagnosis V+, P+, E + SCU
High	Any PRETEXT with M+; AFP level < 100 ng/mL

AFP alpha-fetoprotein, *E* extrahepatic, *M* metastasis, *P* ingrowth portal vein, portal bifurcation, *PFH* pure fetal histology, *PRETEXT* pretreatment extent of disease, *SCU* small-cell undifferentiated type, *V* ingrowth vena cava, all three hepatic veins

Table 18.7 Risk stratification of SIOPEL [37, 38]

Very high risk	Presence of metastatic disease (usually lung) or very low AFP (<100 ng/ml)
High risk	Any tumor not meeting the standard risk or very high-risk criteria
Standard risk	Localized tumors (PRETEXT I, II, or III) with no additional adverse features (e.g., low AFP, vascular involvement (V3 or P2), extrahepatic spread, tumor rupture, metastatic disease, SCU histology, tumor confined to the liver, ≤3 hepatic section involved-PRETEXT I–III, AFP > 100 ng/mL)

AFP alpha-fetoprotein, *C* caudate, *E* extrahepatic, *M* metastasis, *P* ingrowth portal vein, portal bifurcation, *PRETEXT* pretreatment extent of disease, *SCU* small-cell undifferentiated type, *V* ingrowth vena cava, all three hepatic veins, *SIOPEL* Société Internationale d'Oncologie Pédiatrique – Epithelial Liver

prevent the local recurrences, and a re-resection and radiotherapy are not necessary [3, 42].

Preoperative chemotherapy with cisplatin and doxorubicin (PLADO) can effectively shrink the tumor, reduce the size, and give a successful surgical operation option with negative margins and minimal morbidity [42]. Similar resection and survival rates are possible with cisplatin monotherapy for standard risk group with lesser hematologic toxicity than PLADO [41, 43].

PRETEXT stages I and II, with at least a 1-cm safe margin, can undergo primary resection, while all other stages receive neoadjuvant chemotherapy, according to the current

Table 18.8 Treatment modalities according to PRETEXT and POSTTEXT [36]

		PRETEXT	Resection	Neoadjuvant chemotherapy	POSTTEXT	Resection	Transplantation	Adjuvant chemotherapy
COG	+V,+P,+E,+M			+		+		+
					3,+V,+P,−M 4,−M		+	+
	−V,−P,−E,−M	1–2	+					+[a]
		3–4		+	2–3	+		+
					3,+V+P−M 4,−M		+	+
SIOPEL/ GPOH		1–4		+	1–3	+		+
					3,+V+P−M 4,-M		+	+

E extrahepatic, *GPOH* Gesellschaft für pädiatrische Onkologie und Hämatologie, *M* metastasis, *P* ingrowth portal vein, portal bifurcation, *POSTTEXT* posttreatment extent of disease, *PRETEXT* pretreatment extent of disease, *SIOPEL* Société Internationale d'Oncologie Pédiatrique – Epithelial Liver, *V* ingrowth vena cava, all three hepatic veins
aVery low-risk patients (stage 1, pure fetal histology) can be treated with surgery alone

Table 18.9 The criteria to refer the patients for liver transplantation earlier [19]

Multifocal PRETEXT-IV
Solitary PRETEXT-IV; some might be down-staged to PRETEXT-II after neoadjuvant chemotherapy
Unifocal centrally located PRETEXT-II and PRETEXT-III tumors involving main hilar structures (+ P) or all three hepatic veins (+ V)

PRETEXT pretreatment extent of disease

trial of COG AHEP-0731 (Table 18.8) [36, 41]. The GPOH HB 99 trial uses ifosfamide/cisplatin/adriamycin for standard risk (SR) and combination of carboplatin and etoposide in for high-risk (HR) tumors [44].

Liver transplantation and arterial chemoembolization are considered in patients with unresectable tumor after chemotherapy [39]. The criteria to refer the patients for liver transplantation earlier can be seen in Table 18.9 [19].

Outcome

The 5-year survival of hepatoblastoma is 70–80% in children [19]. Survival rates are more than 90% for patients with PRETEXT stage 1–2 tumors and 60% and 20% for PRETEXT stage 3 and 4, respectively [39].

Epithelial Origin

Hepatocellular Carcinoma

Epidemiology

Hepatocellular carcinoma (HCC) is the second most common malignant primary pediatric liver tumor (20–23%) [2, 17–19]. The incidence is 0.29 to 0.45 cases per million children [4, 5]. Mean age is 13.1 ± 1.1 years [21]. The eastern part of Asia and sub-Saharan Africa have the highest incidence rates because of the high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) [45, 46]. Cirrhosis secondary to hepatitis B or C infection, biliary atresia, total parenteral nutrition-associated liver disease, neonatal hepatitis, tyrosinemia, glycogen storage disease type 1, Alagille syndrome, α(alpha)1-antitrypsin deficiency, Neiman-Pick disease, Fanconi's anemia, familial polyposis coli, Gardner's syndrome, focal nodular hyperplasia, and hemochromatosis are some associated conditions with increased hepatocellular carcinoma development risk. However, only 20–35% of children with HCC have an underlying liver disease [47, 48].

Pathology

Histopathological subtypes are classified as [49]:

- Hepatocellular carcinoma adult type and variants
- Fibrolamellar hepatocellular carcinoma
- Transitional liver cell tumor

Clinical Presentation

Right upper quadrant abdominal pain, abdominal distension because of mass effect, weight loss, anorexia, fever, and fatigue are common signs and symptoms. Hepatocellular carcinoma tends to present with advanced disease and metastasizes to local lymph nodes, lungs, and bones.

Diagnosis

AFP levels are elevated in 50–70% at presentation [50]. Radiological investigations show the hepatic mass and metastatic sites. The typical radiological feature of HCC is arterial phase hypervascularization followed by portal/venous phase washout [51]. Anyway, biopsy is your option. In pediatric oncology, biopsy of the liver mass is required to make a diagnosis.

Outcome

The 5-year overall survival (OS) rate is 10–42% for children and adolescents with hepatocellular carcinoma [52, 53] and dependent on the stage of the disease.

Prognostic Factors

Patients with complete surgical resection, resectable PRETEXT group, or localized tumors generally have improved outcomes. However, prognosis in children with HCC is worse than children with hepatoblastoma.

Treatment

Chemotherapy has no place to cure HCC. Complete resection is essential for cure or long-term survival, but children with completely resected hepatocellular carcinoma may also benefit from adjuvant chemotherapy such as cisplatin and doxorubicin [54]. Unfortunately, the survival of patients with advanced disease is still short (one study showing overall survival at 5 years was 28%) [48, 55]. Neoadjuvant chemotherapy or transarterial chemoembolization and radioembolization (yttrium-90) can be used before surgery in patients with unresectable nonmetastatic hepatocellular carcinoma at diagnosis [54, 56]. If tumor is resectable, complete resection must be performed. If tumor is unresectable, orthotropic liver transplantation or transarterial chemoembolization to downsize the tumor can be performed. The Milan criteria are used for liver transplant eligibility. These include one lesion smaller than 5 cm or up to three lesions each smaller than 3 cm, no extrahepatic manifestations, and no vascular invasion [57]. The Barcelona criteria expand these criteria with the following: 1 tumor < 7 cm, 3 tumors < 5 cm, 5 tumors < 3 cm, or down-staging to conventional Milan criteria with pretransplant adjuvant therapies [58]. If the primary tumor is not resectable after neoadjuvant chemotherapy and the liver transplant is not possible, the prognosis is poor. Hepatocellular carcinoma with metastases at diagnosis and recurrent disease are mostly nonresponsive to treatment.

Malignancies of Gastrointestinal Tract

Lymphoid Origin

Primary Gastrointestinal Lymphoma

Epidemiology

Non-Hodgkin lymphomas (NHLs) account for 6–8% of pediatric malignancies [59, 60]. Lymphomas are the second most common tumors (17.2%) among children in Turkey [2]. The incidence of GI lymphoma is 0.19 cases per 100,000 [6] and is the most common GI malignancy. They tend to occur more frequently in the small intestine (terminal ileum), appendix, and cecum [61]. The rate of lymphoma incidence decreases in the distal section of gastrointestinal system. The age range for GI NHLs is 5–15 years with predominance in whites and males (3:1) [6, 62]. Primary and secondary immunodeficiency states, Epstein-Barr virus (EBV) infection, and celiac disease are associated with intestinal lymphomas [63–65].

Clinical Presentation

Painless abdominal mass (81.4%), abdominal swelling and/or mass, vomiting, constipation, diarrhea, intestinal obstruction, and perforation are some of the clinical presentations [66]. Patients with intestinal intussusception are present with acute abdominal pain. Burkitt's lymphoma frequently presents with abdominal pain that mimics acute appendicitis or intussusception [67]. The CNS involvement is 8.8% for Burkitt's lymphoma/Burkitt's leukemia, 5.4% for precursor B-lymphoblastic lymphoma, 3.3% for anaplastic large-cell lymphoma, 3.2% for T-cell-LBL, 2.6% for diffuse large B-cell lymphoma, and not expected for patients with primary mediastinal large B-cell non-Hodgkin lymphoma [68].

Laboratory

Complete blood count (CBC) may be normal. Unexplained anemia, thrombocytopenia, or leukopenia due to extensive bone marrow infiltration, hypersplenism from splenic involvement, or blood loss from gastrointestinal tract involvement and elevated uric acid, potassium, phosphate, and lactate dehydrogenase (LDH) due to high tumor burden can be seen.

Tumor Histology

Lymphoma is diagnosed via Tru-cut biopsy of mass, omental cake or thickness of bowel, bone marrow aspiration, or cytological examination of pleural or peritoneal effusions. In some cases, tissues obtained after surgery such as intussusception, hernia, or appendectomy can reveal lymphoma. Eighty percent of primary intestinal non-Hodgkin lymphomas are of B-cell origin [69]. Burkitt's lymphoma is the prominent pathology in gastrointestinal lymphomas [70]. Diffuse large, marginal zone B-cell, small B lymphocytic, mixed small/large cell, follicular, anaplastic, mature T-cell, and precursor lymphoblastic are other types of primary GI lymphomas [6].

Stage

Contrast-enhanced CT imaging of the neck, chest, abdomen, and pelvis, positron emission tomography (PET), bone marrow aspiration and biopsy, and cerebrospinal fluid examinations are done for routine staging of the disease. Pediatric non-Hodgkin lymphoma is staged according to the Murphy staging system [71]. For abdominal tumors, primary gastrointestinal tumor (completely resected) with or without mesenteric lymph nodes is stage II. However, disseminated

primary intra-abdominal disease and involvement of the bone marrow, central nervous system, or both are evaluated as stage III and stage IV, respectively.

Treatment

Surgery is not advised for advanced cases, since lymphomas are highly sensitive to chemotherapy. Treatment approaches include tumor resection followed by chemotherapy in early stage disease and limited or no resection followed by polychemotherapy in advanced disease [72]. The duration and type of chemotherapy depend on the extent of disease. Total resection of local lymphoma, such as colectomy with lymph node, decreases the stage from III (Group B: COP, COPADM1, COPADM2, CYM1, CYM2; COPADM3) to II (Group A: COPAD, COPAD). Thus, two-cycle chemotherapy used in stage II (Group A) causes less toxicity compared to six cycles of one used in stage III (Group B). Lymphoma malign B (LMB-96) and Berlin-Frankfurt-Munster (BFM-90) have satisfactory results in treatment of B-type lymphoma [73–75].

Epithelial Origin

Esophageal Cancer

Esophageal cancer is a very rare tumor in childhood, and it is much more frequent in males than females [76]. For example, in Turkey's cancer registry data, this cancer type is represented with only 2 cases out of 12,310 pediatric cancers [2]. Chronic irritation such as caustic ingestion or reflux is an important predisposing factor in a long latent period [77]. Esophageal adenocarcinoma (EAC) and squamous cell carcinoma (ESCC) are the two main histologic types [78]. In children, esophageal adenocarcinoma is also associated with Barrett's esophagus. Clinical follow-up of some predisposing factors such as prematurity, cerebral palsy, mental retardation, and hiatal hernia for Barrett's esophagus is recommended. Inherited bone marrow failure syndromes such as Fanconi's anemia, dyskeratosis congenita, and infection with human papilloma virus (HPV) are predisposing conditions for the development of squamous cell carcinomas. Dysphagia and progressive loss of weight are the most common findings at diagnosis. Barium contrast radiography, endoscopy, and biopsy are used for the diagnosis. Esophageal adenocarcinoma has more distant metastasis (46%) than esophageal squamous cell carcinoma (10%) [76]. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system is used for staging [79, 80]. Early diagnosis and surgery can provide long-term survival and favorable outcome in children. Five-year survival rates are 50–80% for stage I and less than 5% for stage IV patients [81]. Preoperative chemotherapy and radiotherapy may provide better survival [76].

Gastric Cancer

Primary gastric tumors are rare and unusual in children. Primary gastric adenocarcinoma (GAC) represents 0.05% of all childhood cancers [82]. Although lifestyle factors or infectious factors such as *Helicobacter pylori*, high salt consumption, smoked food, nitrates and carbohydrates, alcohol consumption, smoking, A blood group, and cancer family history are related to gastric adenocarcinoma in adults [83], the relationship of these factors in children is unknown. However, chronic *H. pylori* gastritis association with pediatric gastric adenocarcinoma is detected [82]. In addition, gene mutations such as non-synonymous coding single-nucleotide variant (SNV) in TP53 may affect inherited risk of cancer in Li-Fraumeni [84].

Symptoms and signs include vague upper abdominal pain, anorexia, dysphagia, hematemesis, anemia, loss of weight, nausea, vomiting, and weakness. Radiologic examination, endoscopy, and biopsy are used for the diagnosis. Thorax and abdominal CT scans and laboratory studies such as CBC and blood chemistry can also be performed. The AJCC TNM system is used for staging [80]. There is no associated tumor marker. CA 19-9 and CEA and CA 72-4 may be high and are associated with poor prognosis [85]. Prognosis depends on the extent of the disease at diagnosis. This can be influenced by its rarity, nonspecific presentation, and delay in diagnosis.

Treatment must include surgical excision with wide margins for localized disease. Surgery will often be a subtotal (distal tumor) or total (proximal tumor) gastrectomy with removal of the associated lymph nodes. A multimodal approach must be considered to improve survival because of frequent recurrences within 2 years of surgery alone [86]. There are American (total and subtotal gastrectomy, chemotherapy, chemoradiotherapy, chemotherapy), European (perioperative chemotherapy, surgery, three cycles chemotherapy), and Asian (surgery and 1-year chemotherapy) protocols to gastric cancer. Preoperative or postoperative adjuvant chemoradiation has been shown to improve survival [87]. Radiation therapy may be used simultaneously with chemotherapeutic agents such as 5-fluorouracil (5-FU) with cisplatin and/or irinotecan in patients with unresectable or incomplete resectable and metastatic tumors. Docetaxel, capecitabine, epirubicin, mitomycin, oxaliplatin, paclitaxel, and novel fluoropyrimidine are some active agents [87–90].

Pancreatic Tumors

Pancreatic malignant tumors are rare in children and adolescents, and the incidence is only 0.46 cases per one million [7]. The most common pancreatic tumors seen in children are the following [91]:

- Solid pseudopapillary tumor of the pancreas: The most common, generally benign pediatric pancreatic tumor.

Female predominance and CD99 staining are some features. Biopsy is not recommended. Total surgery is essential. The prognosis is good following surgery alone. The 5-year survival rate is 95–98%. Gemcitabine is used for unresectable or metastatic disease.

- Pancreatoblastoma: It is the most common pancreatic tumor of young children. Pancreatoblastoma can be associated with Beckwith-Wiedemann syndrome and familial adenomatous polyposis (FAP). It has a high recurrence rate after surgery [92]. The effectiveness of radiation is not known. Cisplatin and doxorubicin are useful in pancreatoblastoma prior to tumor resection [93, 94]. Complete resection is the treatment of choice [93, 94].
- Intraductal papillary mucinous neoplasm: Premalign lesion of the pancreas. There is a recurrent pancreatitis history. Surgery is the mainstay of treatment.
- Primitive neuroectodermal tumor (PNET) of the pancreas: Highly aggressive and poor prognosis. Surgery, chemotherapy, and radiotherapy can be used.
- Pancreatic carcinoma (aciner or ductal): Very, very rare in children. Predisposition syndrome such as familial atypical melanocytic mole melanoma (FAMMM) have 25–40% of CDKN2A mutations and 60–90% and 17% risk rate of melanoma and pancreatic cancer, respectively [95]. Surgery, chemotherapy, and radiotherapy can be used.

Stage, histology, and age are important predictors of pancreas tumor for outcome [7]. Early stage, early diagnosis, complete surgical resection, pancreatoblastoma, and younger age than older ages are some better prognostic factors [7, 94].

Colorectal Carcinoma

Epidemiology

Colorectal cancers are very rare in children. Only 1–4% of all colorectal cancers are seen in individuals younger than 30 years [96]. For example, colorectal tumors are 0.9% of all pediatric neoplasms in children younger than 14 years of age in Turkey [2]. The incidence is 1 per 0.2–1 million in people younger than 20 years [8, 9].

Genetics

Most colon cancers in children occur sporadically. There is no evidence that a family history increases the risk of colon cancer in children. Environmental factors (living in developed countries, smoking) and diet (high fat, low fiber), which are seen less frequently in children and adolescents, play a significant role in colon cancer development. However, genetic predisposition may have a role in the pathogenesis of colorectal carcinoma in children and should always be considered. Lynch syndrome I and II patients have an autosomal dominant trait to develop colon cancer and extracolonic cancers in some families, respectively [97, 98]. Predisposing factors such as inflammatory bowel disease and hereditary polyposis syndromes account for 10% of colon cancers in children [99]. Polyposis syndromes associated with colorectal carcinoma include familial adenomatous polyposis (FAP) and variant FAP syndromes such as Gardner's syndrome, Turcot syndrome, attenuated FAP, hereditary flat adenoma syndrome, Muir-Torre syndrome, hamartomatous polyposis syndromes, Peutz-Jeghers syndrome, juvenile polyposis, and Cowden syndrome. Germline and somatic mutational inactivation of the adenomatous polyposis coli (APC) gene, activation of c-myc and ras oncogenes, and inactivation of tumor suppressor genes such as deleted-in-colorectal-carcinoma (DCC) and P53 can be responsible in the development of colon cancer [100].

Clinical Presentation

The most common symptom is a vague abdominal pain [101]. Others are altered bowel habits, rectal bleeding, decreased appetite, loss of weight, and nausea and vomiting with 3-month median duration of symptoms before diagnosis due to vagueness of symptoms [8, 102, 103]. Abdominal mass and distention, loss of weight, and anemia can be detected in physical examination.

Diagnosis

- Past and family history.
- Evaluation of abdominal complaints.
- Careful physical examination.
- Clinical test:
  - Examination of stool for blood
  - Complete blood count
  - Liver and kidney functions
  - Carcinoembryonic antigen (>5 ng/ml advanced stage and poor prognosis in adults, but minority of pediatric cases may produce due to poorly differentiated tumor)
- Imaging studies:
  - Plain chest radiography
  - Barium enema
  - Abdominal CT or magnetic resonance imaging (MRI)
  - Chest CT and bone scan
  - PET-CT
  - Colonoscopy
- Biopsy via colonoscopy, laparoscopy, or laparotomy.
- Surgical resection of mass and reginal lymph nodes and histology.
- Microsatellite instability (MSI) is a hypermutable phenotype as a result of the loss of DNA mismatch repair activity. Their features are young age, a tendency to develop in the proximal colon, lymphocytic infiltrate, and poorly differentiated, mucinous, or signet ring appearance. The prognosis is better than the patients without MSI [104].

Localization

Adults have a higher prevalence of left-side tumors; however, up to 60% of the tumors in the pediatric population arise on the right side [8, 105]. In another study, the rectosigmoid region was found as a common site for primary tumor [106]. Thus, these tumors may occur at any site in the large bowel. They may spread to the peritoneum, omentum, mesenteric lymph nodes, liver, and ovarium via peritoneal cavity and the lung, brain, and bones via bloodstream [103].

Staging

Biopsy of known enlarged lymph nodes, ovaries in females, resection of the omentum, and the liver are essential for staging. Modified Dukes (A, tumor confined to the bowel wall; B, tumor extension to the serosal fat but without lymph node involvement; C, lymph node involvement; D, distant metastases) and AJCC TNM classifications are used for staging [80]. Children come to medical attention with more advanced disease than adults, with Duke stage C/D or TNM stage III/IV disease [106].

Histology

Pediatric and adolescent age groups have a higher incidence of mucinous adenocarcinoma (40–50%), many with the signet ring cell type [8, 103, 107]. The tumors in younger patients with this histologic variant do not respond well to chemotherapy. The prognosis in children with colorectal carcinoma is poor; 5-year survival rates are as low as 2–5% [108]. Most come with advanced diseases due to late diagnosis [109]. K-ras mutations and other cytogenetic anomalies seen in older patients are frequently lacking in younger patients with noninherited sporadic tumors [110]. K-ras mutation rate (11.1%) was found in Turkish children with colon carcinoma, and all patients with K-ras mutation are older than 12 years old [101].

Treatment

Surgery

Advanced stage and macroscopic tumor due to incomplete resection are significant factors [101]. Laparotomy, complete and careful surgical resection without seeding, and sampling of regional lymph nodes are key components of treatment. Ligating the mesenteric vein is an important manipulation to avoid dissemination of tumor via vein drainage. Children with known polyposis syndromes can often be cured due to early diagnosis by polypectomy during colonoscopy. A safe margin of at least 5 cm of bowel should be removed to minimize the seeding at the anastomotic region. Right hemicolectomy for cecal or right colon tumors, left hemicolectomy for splenic flexure and sigmoid colon tumors, low anterior resection for rectal tumor, and metastasectomy or lobectomy for liver metastases can be performed. Transanal endoscopic microsurgery is another new technique for the treatment [111]. However, children are admitted in more advanced stage, and 30% of them are candidates for curative resection [106]. Debulking surgery has a little benefit in patients with metastatic disease. Resection of bulky tumors or metastases can be performed for palliation.

Adjuvant Treatment

- Chemotherapy
- Radiotherapy (rectal and anal cancer)
- Biological targeted therapy

No adjuvant therapy is recommended after surgery in children with early stage tumors (TNM stage T_{is}, T1–2, N0, M0) due to high 5-year survival rate (over 90%) [112]. However, treatment of Stage II with T3, T4, and N0 is controversial. Stage II patients with pT4 tumors, high histological grade, low MSI, perforation or occlusion, presence of lymphovascular or perineural invasion, less than 12 lymph nodes studied, and undetermined or compromised surgical margins or close margin have a high risk [113, 114]. Mismatch repair (MMR)-deficient colorectal cancers have better prognosis but are resistant to fluorouracil [115].

Unresectable Tumors of Rectum and Anus

Radiotherapy combination with 5-FU-based chemotherapy can be used in rectal and anal cancers. Radiotherapy-induced enteritis can be seen after rectal radiotherapy [116, 117].

Stage II (High Risk) and Stage III (T1–4, N1–2, and M0) Treatment

- FOLFOX 4 (fluorouracil, leucovorin, and oxaliplatin)
- mFOLFOX 6 (fluorouracil, leucovorin, and oxaliplatin plus sunitinib or bevacizumab)
- XELOX (capecitabine and oxaliplatin)

Stage IV Treatment

The majority of the metastatic colorectal cancer patients cannot be cured. The aim of the treatment in these patients includes cure, life prolongation, or palliation. New agents such as capecitabine, oxaliplatin, irinotecan, cetuximab, and bevacizumab are active in advanced disease and are now used in combination for treatment.

Neuroendocrine Origin

Neuroendocrine Tumors of the Gastrointestinal System

Neuroendocrine tumors of the gastrointestinal system are rare. They can produce some vasoactive amines (histamin, serotonin), polypeptides (kallikrein, bradykinin, tachykinin), and prostaglandins, which are responsible for carcinoid syndrome [118].

Epidemiology

Neuroendocrine tumors in children are rare tumors at the rate of 0.08–0.19% [119, 120]. The incidence is rare and changeable and occurs in 1 per 1,000,000 [121, 122]. White and female predominance with a mean age of 12.7 years old are some of the demographic features [120]. They can be sporadic or associated with hereditary conditions such as MEN1, loss of heterozygosity at 11q13 and P53, or adenomatous polyposis coli tumor suppressor gene [10].

Localization

Neuroendocrine tumors are found in different sites of the gastrointestinal tract [123, 124]. The ileum is the most common involvement site with the rate of 45%. The other locations are the rectum (20%), appendix (17%), colon (10.6%), and stomach (7.2%) [123].

Classification

Neuroendocrine tumors arise from enterochromaffin cells. They are classified according to embryonic gut origins such as the foregut (bronchial, stomach), midgut (small intestine, cecum, appendix), and hindgut (distal colon, rectum, genitourinary) [125].

Clinical Presentation

Normally, the serotonin conversion rate from dietary tryptophan is 1%, but this rate is increased to 70% or more in neuroendocrine tumor with tryptophan hydroxylase and aromatic L-amino acid decarboxylase. Serotonin is then metabolized to 5-hydroxyindoleacetic acid (HIAA) with monoamine oxidase and aldehyde dehydrogenase [126]. Neuroendocrine tumors of the midgut such as jejunum, ileum, and cecum and ovaries have a higher risk for carcinoid syndrome than the pancreas, colon, and anus because of the high metastases risk of midgut tumors to the liver and secretion of tumor products into the systemic circulation before liver-inactivating first-pass effect [127]. Symptoms are related to liver metastasis of the tumor, because serotonin secreted from the GIS is eliminated by normal liver tissue fast, but not by metastatic liver. In addition, 5-hydroxytryptophan (and histamin) is produced by foregut neuroendocrine tumors due to a lack of aromatic amino acid decarboxylase instead of serotonin. Bioactive hormones such as serotonin are rarely secreted by the hindgut [128]. Flushing, tachycardia, diarrhea, hypotension, venous telangiectasia, and wheezing due to bronchospasm are the symptoms of carcinoid syndrome. They can be found incidentally after appendectomy and rectal examination in the appendix with or without right lower quadrant pain at the rate of 2.5/1000 [129]. Abdominal pain and/or intermittent obstruction in small bowel neuroendocrine tumors and changes in bowel habit, obstruction or bleeding in the colon, and rectal and anal neuroendocrine tumors are the other clinical presentations.

Pathology

Histology of the tumor should be evaluated carefully for the clinical decision-making. Histologically, they are divided into two main categories: (1) well and (2) poorly differentiated (Table 18.10) [130–134].

Laboratory

Baseline levels of some laboratory markers may be useful before surgery or biopsy to follow up the patient:

- Chromogranin A
- Pancreastatin
- 24-hour urine 5-hydroxyindoleacetic acid
- Serotonin, gastrin, neuron-specific enolase, neurokinin A

Radiology

- Endoscopy
- CT or MRI of the primary tumor location
- Somatostatin receptor (subtypes 1–5) scintigraphy
- 111 In-DTPA-octreotide combination with CT (single photon emission CT)
- 68Ga-dodecanetetraacetic acid (DOTA)-tyrosine 3-octreotide (DOTATOC) for subtypes 2 and 5 with PET
- 68Ga-DOTA-1-Nal3-octreotide (DOTANOC) for subtypes 2, 3, and 5 with PET
- 68Ga-DOTA-tyrosine-3-octreotate (DOTATATE) for subtypes 2 with PET

Table 18.10 Classification of gastrointestinal neuroendocrine tumors [130]

Differentiation	Grade	Mitotic count	Ki-67	Traditional	ENETS, WHO
Well-differentiated	Low (G1)	<2 per 10 HPF	<3%	Carcinoid, islet cell, pancreatic (neuro) endocrine tumor	Neuroendocrine tumor, grade 1
	Intermediate (G2)	2–20 per 10 HPF	3–20%	Carcinoid, atypical carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, grade 2
Poorly-differentiated	High (G3)	>20 per 10 HPF	>20%	Small-cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell
				Large-cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell

ENETS European Neuroendocrine Tumor Society, *WHO* World Health Organization, *HPF* high-power field

Treatment Principles

- Localization and staging
- Histological grade and differentiation
- Surgical removal of tumor, if feasible, and carcinoid crisis
- Control of symptoms of carcinoid syndrome
- Antitumor therapy for unresectable metastatic disease

Surgery According to Extent of Disease

- Local tumor: Resection that depends on the site and size of tumor is strongly recommended.
- Metastatic tumor: Resection may be advised for the palliation of obstruction, bleeding, and pain related to primary tumor.

Treatment According to Localization [135]

Appendix

Simple appendectomy is sufficient for small (<1.5 cm), localized tumors without atypical and invasive histology and without positive surgical margins.

Larger (≥2 cm) tumors with atypical histology or positive margins:

- Lymph node sampling.
- Ileocecal resection.
- Right hemicolectomy: This is recommended in completely resected appendicular neuroendocrine tumors only for tumors larger than 1.5 cm [122]. This practice remains controversial, because there are no reported cases of recurrence in children and adolescents after resection without right hemicolectomy.

Any tumor without distant metastases should be completely resected.

Small Bowel

Despite metastatic disease of the ileal site, resection of involved segment and small bowel mesentery is necessary because fibrosis develops in unresected site of the ileum. Malabsorption is the major problem [136].

Ampulla of Vater

Pancreaticoduodenectomy regardless of size.

Rectal Neuroendocrine Tumor

Metastases are seen in 2% of patients with tumors smaller than <1 cm, 10–15% in patients with tumors measuring 1.0–1.9 cm, and 60–80% in tumors larger than >2 cm [137]:

- Smaller than 1 cm and confined to the mucosa or submucosa; local endoscopic excision can be performed if they lack other risk factors, i.e., mitotic rate >2 per 10 high-power fields (HPF) or lympho-vascular invasion.
- 1 to 1.9 cm confined to the mucosa or submucosa; transanal resection or advanced endoscopic resection in patients without risk factors, whereas radical resection may be more appropriate for tumors with risk factors.
- For tumors more than 2 cm that invade into or beyond muscularis propria, radical surgical resection must be performed [138].

Other Treatment Modalities

- Somatostatin analogs (111 indium-octreotide, yttrium-90 DOTATOC, 177-Lu-octreotate)
  - Residual disease and significant symptoms due to carcinoid syndrome
  - Subcutaneous injection daily to monthly
- Interferon alpha
  - It is used in patients with indolent disease, but side effects are the main problem in clinical practice.
- Chemotherapy
  - They are generally not effective in these tumors.
  - Patients with higher Ki-67 levels respond well to chemotherapy compared to patients with lower levels (<2%)
  - In adult series, 5-FU, cisplatin, doxorubicin, dacarbazine, and combination of these agents are used.

Liver Transplantation

Hepatic embolization (chemoembolization).

Pancreatic Neuroendocrine Tumor

- Functional tumors: The most common type is insulinoma (most are benign), followed by gastrinoma (most are malign). ACTHoma and VIPoma are seldom [139].
- Nonfunctional tumors: They are associated with MEN1 [140].
- Insulinoma:
  - Insulinomas are the second most common tumor of the pancreas in children. It has a benign nature. Incidence of malignancy is 6%. MRI is the first imaging method; however, in case of failure to detect, PET-CT can be successfully used for identification. Pancreas-sparing surgery can be preferred [91].
  - For malignant tumors with unresectable or metastatic disease, chemotherapy and mammalian target of rapamycin (mTOR) inhibitors can be used [11, 139].

Follow-Up

Patients with local, small, and complete surgical resection should be followed up closely for recurrence with baseline levels of some markers. History, physical examination, monitorization of the tumor markers, and appropriate local imag-

ing studies (CT, MRI) are recommended for all patients. Proctoscopy is recommended in patients with rectal tumors ≥2 cm within the 6–12-month intervals. Patients with appendiceal tumors ≤2 cm are generally not required to be followed up. Tumors of other sites are followed up in regular intervals. In addition, cardiac evaluation and monitoring should be done for neuroendocrine tumoral heart disease. Neuroendocrine tumors also may produce ectopic ACTH and cause Cushing's disease [141].

Mesenchymal Origin

Gastrointestinal Stromal Tumor

Epidemiology

Gastrointestinal stromal tumors (GISTs) that originate from mesenchyme (connective tissue) are the most common gastrointestinal sarcoma in adults with a rate of 0.2% of all GI tumors and 80% of GI sarcomas [12]. However, these are rare tumors in pediatric age. The annual incidence is 0.02–0.08 per million in children younger than 14 years of age [142, 143]. The percentage of patients with GIST below the age of 21 years is 0.5–2.7% [144–146]. They account for approximately 2.5% of all non-rhabdomyosarcomatous soft tissue sarcomas in children [147]. They are mostly found in the gastric locale and most commonly occur in adolescent girls [148, 149].

Pathogenesis

GISTs have an expression of the CD117 antigen, which is part of the KIT transmembrane receptor tyrosine kinase, which is a product of KIT proto-oncogene. Abnormal activated KIT protein and oncologic signal in the cell are triggered by this mutation [150]. Some GISTs without KIT mutations have active mutations in another related tyrosine kinase, the platelet-derived growth factor receptor alpha (PDGFRA) [151]. Mutations are 67.9% on exon 11, 18.1% on exon 9, 1.6% on exon 13, and 1.6% on exon 17 in KIT and 3.9% on exon 18 and 0.8% on exon 12 in PDGFRA [152]. Mutation in the KIT and PDGFRA gene is found in 85% in adults; however, this rate is 15% in pediatric cases [148]. In addition, somatic and germline succinate dehydrogenase (SDH) genes B, C, and D mutations are described in children [153]. But loss of function mutation of SDH gene A might be associated with features of a tumor suppressor gene [154, 155]. Because of high and amplified insulin-like growth factor 1 receptor (IGF1R) expression, IGF1R inhibitor might be potentially therapeutic for these patients [156].

Risk Factors

Pediatric GISTs are associated with some tumor predisposition syndromes:

- Carney triad [157]
  - GIST, pulmonary chondromas, and paragangliomas
  - Other conditions such as adrenal adenomas, esophageal leiomyomas, and pheochromocytomas
  - Absence of KIT, PDGFRA, and SDH mutations
- Carney-Stratakis syndrome [153]
  - Paraganglioma and GIST
  - 12% of pediatric GISTs
  - Somatic and germline mutations of the succinate dehydrogenase (SDH) genes B, C, and D
  - Absence of KIT or PDGFRA mutation
- Familial GIST [158]
  - Heritable point mutation of KIT gene
  - Multiple gastrointestinal GISTs
  - Diffuse interstitial cells of Cajal (ICC) hyperplasia as precursor lesion both in sporadic and familial GISTs [159]
- Neurofibromatosis 1-associated GIST [160, 161]
  - The most common site of primary lesions is small bowel (75%).
  - Frequently multiple.
  - High or intermediate risk and poor prognosis.
  - ICC hyperplasia.
  - Mostly absence of KIT and PDGFRA mutation except in a few cases.
  - SDH subunit B expression is positive [162].

Histopathology

GISTs have two major histologic patterns: spindle cell and epithelioid. Pediatric GISTs have a predominance of the epithelioid [163].

Clinical Presentation

The most common primary sites are the stomach (60%) and jejunum-ileum (30%). GISTs can occur in any portion of the alimentary tract such as the duodenum, colon, rectum, appendix, omentum, and extra-gastrointestinal sites such as retroperitoneum and mesentery [164].

Gastrointestinal bleeding is the most common presentation, which could be acute or chronic. Acute bleeding-related melena, hematemesis, and chronic bleeding-related anemia, weakness, and syncope are detected. Anemia is the most common presentation of chronic bleeding [165, 166]. In addition, acute abdomen owing to rupture, obstruction of bowel, abdominal pain, and swelling are the other presentations. Sometimes they are detected incidental due to asymptomatic clinic.

Presentation occurs during the second decade of life with female predominance, high propensity for multifocality, nodal metastases, and high incidence of local recurrence, but indolent courses are some other clinical features [148, 166].

They frequently metastasize to the liver and disseminate via the abdominal cavity to the peritoneum, but lung and bone metastasis are uncommon [163, 167].

Prognostic Factors

Mitotic index and size can be used in risk stratification of primary GISTs according to localization from very low risk to high risk [168]. Tumor rupture, which impacts negatively on disease-free survival, is an independent risk factor and is added to modified risk stratification in the high-risk category [169].

Diagnosis/Staging

- Esophago-gastro-duodeno barium graphy
- Ultrasonography
  - Suspicious lesion can be detected with these diagnostic tools.
- Contrast-enhanced computerized tomography (CT)
  - Preferred for screening and staging
- Magnetic resonance imaging (MRI)
  - Preferred for specific sites
  - Better definition for surgery
  - Contraindication to contrast
- Upper endoscopy
  - Features of submucosal mass of GISTs can be evaluated.
- Endoscopic ultrasonography and fine-needle aspiration
  - Cytologic analysis, immunohistochemistry, polymerase chain reaction (PCR) for KIT mutations
  - Sensitivity 82%, specificity 100% [170]
- PET-CT
  - High sensitivity, but not specific
  - Monitor the response to therapy

There is no staging system for pediatric GISTs. TNM and alternative risk stratification systems for GISTs might be used.

Refer to genetic counselor for all pediatric patients with wild-type GISTs.

Outcome

Estimation of survival in the pediatric population is difficult due to the rarity of this tumor. Pediatric GISTs have an indolent course. In one study, despite metastasis with the rate of 65%, only 1 patient died in 17 cases [166]. In another series, 6 patients died with a median survival of 16 years in 44 cases [165].

Treatment

A multidisciplinary team including pediatric oncologist, pediatric surgeon, pathologist, and radiologist is mandatory for the treatment. All samples must be analyzed for the mutations of KIT, PDGFR, and BRAF (V600E). Chemotherapy and radiotherapy are ineffective in GIST [171].

- GIST with a KIT or PDGFR mutation
  - Completely resected tumor
    - History and physical examination every 3–6 months and then annually
    - CT scan every 3–6 months for 3–5 years and then annually
  - More locally advanced or metastatic disease
    - Imatinib
    - History and physical examination as well as abdominopelvic CT scan every 3–6 months
- Wild-type GIST (no mutation) [163]
  - Non-metastatic tumors
    - Complete gross surgical resection with an intact pseudocapsule and negative margins.
    - Wedge resection if feasible, because total gastrectomy may not prevent recurrence.
    - Lymph node sampling because of high incidence of nodal involvement.
    - Adjuvant imatinib is not recommended.
  - Asymptomatic unresectable or metastatic disease
    - Followed by physical examination and imaging.
    - Baseline images – such as chest radiography, CT or MRI of the abdomen and pelvis, and PET-CT – are performed and repeated in 6 weeks.
    - In patients with stable clinic, chest radiograph, CT or MRI of the abdomen and pelvis at 3-month intervals for 24 months followed by visits at 6-month intervals for 24 months and yearly thereafter.
  - Unresectable or metastatic disease with progression or clinical symptoms.
    - Surgical resection ideally with negative margins or without negative margins, if feasible.
    - The risk of benefits should be evaluated on a case-by-case basis.
    - Tyrosine kinase inhibitor therapy should be initiated in patients without complete resection.
  - Asymptomatic multiple recurrent tumors
    - Tyrosine kinase therapy should be considered.
    - Tyrosine kinase inhibitors: Doses of imatinib within 260 and 340 mg/m^2 provide similar clinical benefit like in adults treated with daily doses of 400 mg and 600 mg, respectively [172].

Imatinib benefit is restricted to KIT exon 11 and PDGFRA mutations and cannot be recommended in patients with wild-type mutations. Partial response and disease stabilization with imatinib and sunitinib can be achieved in pediatric patients with wild-type mutations.

References

1. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol. 2010;28(15):2625–34.
2. Kutluk MT, Yeşilipek A. Turkish national pediatric cancer registry 2002–2008 (Turkish pediatric oncology group and Turkish pediatric hematology society). J Clin Oncol. 2013;31(suppl):abstr 10067.
3. Perilongo G, Shafford E, Plaschkes J. SIOPEL trials using preoperative chemotherapy in hepatoblastoma. Lancet Oncol. 2000;1:94–100.

4. Darbari A, Sabin KM, Shapiro CN, Schwartz KB. Epidemiology of primary hepatic malignancies in U.S. children. Hepatology. 2003;38(3):560–6.
5. Mann JR, Kasthuri N, Raafat F, Pincott JR, Parkes SE, Muir KR, et al. Malignant hepatic tumours in children: incidence, clinical features and aetiology. Paediatr Perinat Epidemiol. 1990;4(3):276–89.
6. Kassira N, Pedroso FE, Cheung MC, Koniaris LG, Sola JE. Primary gastrointestinal tract lymphoma in the pediatric patient: review of 265 patients from seer registry. J Pediatr Surg. 2011;46:1956–64.
7. Brecht IB, Schneider DT, Kloppel G, von Schweinitz D, Barthlen W, Hamre MR. Malignant pancreatic tumors in children and young adults: evaluation of 228 patients identified through the Surveillance, Epidemiology, and End Result (SEER) database. Klin Padiatr. 2011;223(6):341–5.
8. Saab R, Furman WL. Epidemiology and management options for colorectal cancer in children. Paediatr Drugs. 2008;10(3):177–92.
9. Kravarusic D, Feigin E, Dlugy E, Steinberg R, Baazov A, Erez I, et al. Colorectal carcinoma in childhood: a retrospective multicenter study. J Pediatr Gastroenterol Nutr. 2007;44(2):209–11.
10. Oberg K. Diagnosis and treatment of carcinoid tumors. Expert Rev Anticancer Ther. 2002;3:863–77.
11. Ding L, Yin Y, Han L, Li Y, Zhao J, Zhang W. TSC1-mTOR signaling determines the differentiation of islet cells. J Endocrinol. 2017 Jan;232(1):59–70.
12. Miettinen M, Lasota J. Gastrointestinal Stromal Tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics. Pol J Pathol. 2003;54(1):3–24.
13. Pickett LK, Briggs HC. Cancer of the gastrointestinal tract in childhood. Pediatr Clin N Am. 1967;14:223–34.
14. Bethel CAI, Bhattacharyya N, Hutchinson C, Ruymann F, Cooney DR. Alimentary tract malignancies in children. J Pediatr Surg. 1997;32:1004–9.
15. Ladd AP, Grossfeld JL. Gastrointestinal tumors in children and adolescents. Semin Pediatr Surg. 2006;15:37–47.
16. Kutluk T, Yalcin B, Ekinci S, Kale G, Akyuz C, Aydin B, et al. Primary liver tumors in children: Hacettepe experience. Turk J Pediatr. 2014;56:1–10.
17. Stocker JT. Hepatic tumors in children. Clinics Liver Dis. 2001;5:259–81.
18. Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. Hum Pathol. 1983;14:512–37.
19. Agarwala S. Primary malignant liver tumors in children. Indian J Pediatr. 2012;79(6):793–800.
20. Schnater JM, Kohler SE, Lamers WH, Von Schweinitz D, Aronson DC. Where do we stand with hepatoblastoma? Cancer. 2003;98:668–78.
21. Pham TH, Iqbal CW, Grams JM, Zarroug AE, Wall JC, Ishitani MB, et al. Outcomes of primary liver cancer in children: an appraisal of experience. J Pediatr Surg. 2007;42(5):834–9.
22. Turcotte LM, Georgieff MK, Ross JA, Feusner JH, Tomlinson GE, Maglogolowkin MH, et al. Neonatal medical exposures and characteristics of low birth weight hepatoblastoma cases: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2014;61(11):2018–23.
23. Meyers R, Aronson DC, Von Schweinitz D, Zimmermann A, Malogolowkin MH. Pediatric liver tumors. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 6th ed. Philadephia: Wolters Kluwer and Lippincott Williams; 2011.
24. Ehrlich P, Greenberg M, Filler RM. Improved long term survival with preoperative chemotherapy for hepatoblastoma. J Pediatr Surg. 1997;32:999–1003.
25. Weinblatt M, Siegel S, Siegel M, Stanley P, Weitzman JJ. Preoperative chemotherapy for unresectable primary hepatic malignancy in children. Cancer. 1982;50:1031–4.
26. De Ioris M, Brugieres L, Zimmermann A, Keeling JW, Brock P, Maibach R, et al. Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: the SIOPEL group experience. Eur J Cancer. 2008;44:545–50.
27. Miller J, Greenspan B. Integrated imaging of hepatic tumors in children: I. Malignant lesions (primary and metastatic). Radiology. 1985;145:83–90.
28. Perilongo G, Brown J, Shafford E, Brock P, De Camargo B, Keeling JW, et al. Hepatoblastoma presenting with lung metastases. Cancer. 2000;89:1845–53.
29. Maruyama K, Ikeda H, Koizumi T, Tsuchida Y, Tanimura M, Nishida H, et al. Case-control study of perinatal factors and hepatoblastoma in children with extremely low birth weight. Pediatr Int. 2000;42:492–8.
30. Hiyama E, Yamaoka H, Matsunaga T, Hayashi Y, Ando H, Suita S, et al. High expression of telomerase is an independent prognostic indicator of poor outcome in hepatoblastoma. Br J Cancer. 2004;91:972–9.
31. Chitraghar S, Iyer VK, Agarwala S, DattaGupta S, Sharma A, Wari MN. Loss of heterozygosity on chromosome 11p15.5 and relapse in hepatoblastoma. Eur J Pediatr Surg. 2011;21:50–3.
32. Litten JB, Tomlinson GE. Liver tumors in children. Oncologist. 2008;13(7):812–20.
33. Nathan JD, Ryckman FC, Alonso MH, Tiao G. Transplantation for hepatic malignancy in children. In: Bussuttil RW, Klintmalm GBG, editors. Transplantation of the liver. 3rd ed. Philadelphia: Elsevier Saunders; 2015. p. 346–58.
34. Roebuck DJ, Aronson D, Clapuyt P, Czauderna P, De Ville De Goyet J, Gauthier F, et al. 2005 pretext: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. Pediatr Radiol. 2007;37:123–32.
35. Meyers RL, Tiao G, de Ville de Goyet J, Superina R, Aronson DC. Hepatoblastoma state of the art: pre-treatment extent of disease, surgical resection guidelines and the role of liver transplantation. Curr Opin Pediatr. 2014;26(1):29–36.
36. Meyers RL, Aronson DC, Zimmermann A. Malignant liver tumors. In: CA G, Adzick NS, Krummel TM, Laberge JM, Shamberger R, Caldamone A, editors. Pediatric surgery. Philadelphia: Saunders, an imprint of Elsevier Inc.; 2012. p. 463–82.
37. Aronson DC, Czauderna P, Maibach R, Perilongo G, Morland B. The treatment of hepatoblastoma: its evolution and the current status as per the SIOPEL trials. J Indian Assoc Pediatr Surg. 2014;19(4):201–7.
38. SIOPEL. SIOPEL guidelines for the treatment of hepatoblastoma. 2018; Available from: http://www.siopel.org/?q=node/157.
39. Czauderna P, Otte JB, Aronson DC, Gauthier F, Mackinlay G, Roebuck D, et al. Childhood liver tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Guidelines for surgical treatment of hepatoblastoma in the modern era–recommendations from the childhood liver tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Eur J Cancer. 2005;41:1031–6.
40. Zsiros J, Brugieres L, Brock P, Roebuck DJ, Maibach R, Zimmermann A, et al. Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): a prospective, single-arm, feasibility study. Lancet Oncol. 2013;14(9):834–42.
41. Perilongo G, Maibach R, Shafford E, Brugieres L, Brock P, Morland B, et al. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med. 2009;22(361):1662–70.
42. Schnater JM, Aronson DC, Plaschkes J, Perilongo G, Brown J, Otte JB, et al. Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the

International Society of Pediatric Oncology Liver Tumor Study Group. Cancer. 2002;94:1111–20.
43. Anonymous. Risk-based therapy in treating younger patients with newly diagnosed liver cancer. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00980460.
44. Von Schweinitz D, Haberle B. German liver tumor study: Hb 99. First International Symposium Childhood Hepatoblastoma; Poland, Gdansk, 2007.
45. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med. 1997;336(26):1855–9.
46. Chen DS. Hepatitis B vaccination: the key towards elimination and eradication of hepatitis B. J Hepatol. 2009;50(4):805–16.
47. Hadley GP, Govender D, Landers G. Primary tumors of the liver in children: an African perspective. Pediatr Surg Int. 2004;20:314–8.
48. Czauderna P, MacKinley G, Perilongo G, Brown J, Shafford E, Aronson D, et al. Hepatocellular carcinoma in children: results of the first prospective study of the International Society of Pediatric Oncology Group. J Clin Oncol. 2002;20:2798–804.
49. Zimmermann A. Hepatoblastoma with cholangioblastic features ('cholangioblastic hepatoblastoma') and other liver tumors with bimodal differentiation in young patients. Med Pediatr Oncol. 2002;39:487–91.
50. Grosfeld JL, Otte JB. Liver tumors in children. In: Carcahi R, Grosfeld JL, Azmy AF, editors. The surgery of childhood tumors. 2nd ed:. Berlin, Heidelberg: Springer; 2008. p. 227–226A.
51. Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut. 2010;59(5):638–44.
52. Anonymous. Childhood cancer by the ICCC. In: Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al., editors. Seer cancer statistics review, 1975–2012 (vintage 2009 populations). Bethesda: National Cancer Instute; 2012.
53. Yu SB, Kim HY, Eo H, Won JK, Jung SE, Park KW, et al. Clinical characteristics and prognosis of pediatric hepatocellular carcinoma. World J Surg. 2006;30:43–50.
54. Schmid I, von Schweinitz D. Pediatric hepatocellular carcinoma: challenges and solutions. J Hepatocell Carcinoma. 2017;4:15–21.
55. Katzenstein HM, Krailo MD, Malogolowkin MH, Ortega JA, Liu-Mares W, Douglas EC, et al. Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group Intergroup Study. J Clin Oncol. 2002;20(12):2789–97.
56. Hawkins CM, Kukreja K, Geller JI, Schatzman C, Ristagno R. Radioembolisation for treatment of pediatric hepatocellular carcinoma. Pediatr Radiol. 2013;43(7):876–81.
57. Kim JM, Kwon CH, Joh JW, Kim SJ, Shin M, Kim EY, et al. Patients with unresectable hepatocellular carcinoma beyond Milan criteria: should we perform transarterial chemoembolization or liver transplantation? Transplant Proc. 2010;42(3):821–4.
58. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329–38.
59. Oschlies I, Klapper W, Zimmermann M, Krams M, Wacker HH, Burkhardt B, et al. Diffuse large B-cell lymphoma in pediatric patients belongs predominantly to the germinal-center type B-cell lymphomas: a clinicopathologic analysis of cases included in the German BFM (Berlin-Frankfurt-Munster) multicenter trial. Blood [Multicenter Study Research Support, Non-U.S. Gov't]. 2006;107(10):4047–52.
60. Jaffe E, Harris NL, Stein H, et al. Introduction and overview of the classification of the lymphoid neoplasms. In: Swerdlow S, Campo E, Harris NL, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. International Agency for Research on Cancer: Lyon; 2008. p. 157–66.
61. Radman I, Kovacevic-Metelko J, Aurer I, Nemet D, Zupancic-Salek S, Bogdanic V, et al. Surgical resection in the treatment of primary gastrointestinal non-Hodgkin's lymphoma: retrospective study. Croat Med J. 2002;43:555–60.
62. Bethel CA, Bhattacharyya N, Hutcinson C, Ruymann F, Cooney DR. Alimentary malignancies in children. J Pediatr Surg. 1997;32:1004–8.
63. Smets F, Sokal EM. Lymphoproliferation in children after liver transplantation. J Pediatr Gastroenterol Nutr. 2002;34:499–505.
64. Purtillo DT, DeFlorio D, Hutt LM, Bhawan J, Yang JPS, Otto R, et al. Variable phenotype expression of an X-linked lymphoproliferative syndrome. N Engl J Med. 1977;297:1077–80.
65. Pricolol VE, Mangi AA, Aswad B, Bland KI. Gastrointestinal malignancies in patients with celiac sprue. Am J Surg. 1998;176:344–7.
66. Morsi A, Abd El-Ghani Ael G, El-Shafiey M, Fawzy M, Ismail H, Monir M. Clinico-pathological features and outcome of management of pediatric gastrointestinal lymphoma. J Egypt Natl Canc Inst. 2005;17(4):251–9.
67. Percy CL, Smith MA, Linet M, et al. Cancer incidence and survival among children and adolescents: United States seer program 1975–1995. Bethesda: National Cancer Institute; 1999.
68. Salzburg J, Burkhardt B, Zimmermann M, Wachowski O, Woessmann W, Oschlies I, et al. Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: a Berlin-Frankfurt-Munster Group report. J Clin Oncol. 2007;25(25):3915–22.
69. Guillerman RP. Primary intestinal non-Hodgkin lymphoma. J Pediatr Hematol Oncol. 2000;22:476–8.
70. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol. 1999;17(12):3835–49.
71. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol. 1980;7(3):332–9.
72. Bandyopadhyay R, Sinha SK, Chatterjee U, Nag D, Mukhopadhyay S, Chowdhury SR, et al. Primary pediatric gastrointestinal lymphoma. Indian J Med Paediatr Oncol. 2011;32(2):92–5.
73. Patte C, Auperin A, Gerrard M, Michon J, Pinkerton R, Sposto R, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. Blood [Multicenter Study Randomized Controlled Trial Research Support, NIH, Extramural Research Support, Non-US Gov't]. 2007;109(7):2773–80.
74. Patte C, Auperin A, Michon J, Behrendt H, Leverger G, Frappaz D, et al. The Societe Francaise d'Oncologie Pediatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood [Clinical Trial Research Support, Non-U.S. Gov't]. 2001;97(11):3370–9.
75. Woessmann W, Seidemann K, Mann G, Zimmermann M, Burkhardt B, Oschlies I, et al. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. Blood [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2005;105(3):948–58.

76. Issaivanan M, Redner A, Weinstein T, Soffer S, Glassman L, Edelman M, et al. Esophageal carcinoma in children and adolescents. J Pediatr Hematol Oncol. 2012;34(1):63–7.
77. Kaye M, Willie R. Caustic ingestions in children. Curr Opin Pediatr. 2009;21:651–4.
78. Daly JM, Fry WA, Little AG, Winchester DP, McKee RF, Stewart AK, et al. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. J Am Coll Surg. 2000;190:562–72.
79. McNamara MJ, Adelstein DJ. Current developments in the management of locally advanced esophageal cancer. Curr Oncol Rep. 2012;14(4):342.
80. Amin MB, Edge S, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. AJCC cancer staging manual. 8th ed. NewYork: Springer; 2017.
81. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349:2241–52.
82. Harting MT, Blakely ML, Herzog CE, Lally KP, Ajani JA, Andrassy RJ. Treatment issues in pediatric gastric adenocarcinoma. J Pediatr Surg. 2004;39(8):e8–10.
83. Milne AN, Carneiro F, O'Morain C, Offerhaus GJ. Nature meets nurture: molecular genetics of gastric cancer. Hum Genet. 2009;126(5):615–28.
84. Chang VY, Federman N, Martinez-Agosto J, Tatishchev SF, Nelson SF. Whole exome sequencing of pediatric gastric adenocarcinoma reveals an atypical presentation of Li-Fraumeni syndrome. Pediatr Blood Cancer. 2013;60(4):570–4.
85. Ychou M, Duffour J, Kramar A, Gourgou S, Grenier J. Clinical significance and prognostic value of CA72-4 compared with CEA and ca19-9 in patients with gastric cancer. Dis Markers. 2000;16(3–4):105–10.
86. Mlkvy P. Multimodal therapy of gastric cancer. Dig Dis. 2010;28(4–5):615–8.
87. Varadhachary G, Ajani JA. Preoperative and adjuvant therapies for upper gastrointestinal cancers. Expert Rev Anticancer Ther. 2005;5(4):719–25.
88. Ajani JA. Current status of therapy for advanced gastric carcinoma. Oncology. 1998;12(8 Suppl 6):99–102.
89. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (spirits trial): a phase III trial. Lancet Oncol. 2008;9(3):215–21.
90. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. Crit Rev Oncol Hematol. 2009;71(2):127–64.
91. Hsieh L, Burjonrappa S. Pediatric pancreatic tumors: a review of current concepts. JOP J Pancreas (Online). 2016;17(3):257–62.
92. Rojas Y, Warneke CL, Dhamne CA, Tsao K, Nuchtern JG, Lally KP, et al. Primary malignant pancreatic neoplasms in children and adolescents: a 20 year experience. J Pediatr Surg [Comparative Study Multicenter Study]. 2012;47(12):2199–204.
93. Glick RD, Pashankar FD, Pappo A, Laquaglia MP. Management of pancreatoblastoma in children and young adults. J Pediatr Hematol Oncol. 2012;34(Suppl 2):S47–50.
94. Klimstra DS, Wenig BM, Adair CF, Heffess CS. Pancreatoblastoma. A clinicopathologic study and review of the literature. Am J Surg Pathol. 1995;19(12):1371–89.
95. McWilliams RR, Wieben ED, Rabe KG, Pedersen KS, Wu Y, Sicotte H, et al. Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling. Eur J Hum Genet [Research Support, N.I.H., Extramural]. 2011 Apr;19(4):472–8.
96. Hoerner MT. Carcinoma of the colon and rectum in persons under 20 years of age. Am J Surg. 1958;96:47–53.
97. Fitzgibbons RJ, Lynch HT, Stanislav GV, Watson PA, Lanspa SJ, Marcus JN, et al. Recognition and treatment of patients with hereditary nonpolyposis colon cancer (Lynch syndromes I and II). Ann Surg. 1987;206(3):289–95.
98. Aiges HW, Kahn E, Silverberg M, Daum F. Adenocarcinoma of the colon in an adolescent with the family cancer syndrome. J Pediatr. 1979;94:632–3.
99. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-update based on new evidence. Gastroenterology. 2003;124:544–60.
100. Hamilton SR, Vogelstein B, Kudo S, Riboli E, Nakamura S, Hainaut P, et al. In: Hamilton SR, Aaltonen LA, editors. Tumors of the colon and rectum. Lyon: IARC Press; 2000.
101. Akyuz C, Buyukcam A, Orhan D, Kutluk T, Yalcin B, Varan A, et al. K-RAS mutation and colorectal carcinoma in childhood. Pediatr Blood Cancer. 2012;59(6):965–1152.
102. Pappo A, Rodriguez-Galindo C, Furman W. Management of infrequent cancers of childhood. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 6th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2011. p. 1098–123.
103. Hill DA, Furman WL, Billups CA, Riedley SE, Cain AM, Rao BN, et al. Colorectal carcinoma in childhood and adolescence: a clinicopathologic review. J Clin Oncol. 2007;25(36):5808–14.
104. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology. 2010;138(6):2073–87.
105. Sultan I, Rodriguez-Galindo C, El-Taani H, Pastore G, Casanova M, Gallino G, et al. Distinct features of colorectal cancer in children and adolescents: a population-based study of 159 cases. Cancer. 2010;116(3):758–65.
106. Karnak I, Ciftci AO, Senocak ME, Buyukpamukcu N. Colorectal carcinoma in children. J Pediatr Surg. 1999;34:1499–504.
107. Ferrari A, Rognone A, Casanova M, Zaffignani E, Piva L, Collini P, et al. Colorectal carcinoma in children and adolescents: the experience of the Istituto Nazionale Tumori of Milan, Italy. Pediatr Blood Cancer. 2008;50(3):588–93.
108. Andersson A, Bergdahl L. Carcinoma of the colon in children: a report of six new cases and review of the literature. J Pediatr Surg. 1976;11:967–71.
109. Lin JT, Wang WS, Yen CC, Liu JH, Yang MH, Chao TC, et al. Outcome of colorectal carcinoma in patients under 40 years of age. J Gastoent Hepatol. 2005;20:900–5.
110. Bleyer A, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B, et al. The distinctive biology of cancer in adolescents and young adults. Nat Rev Cancer. 2008;8(4):288–98.
111. Shah N, Sasikumar P, Rajkumar JS. Single incision laparoscopic surgery-trans anal endoscopic microsurgery: a technological innovation. J Minim Access Surg. 2014;10(2):99–101.
112. Compton CC. Colorectl carcinoma: diagnostic, prognostic, and molecular features. Mod Pathol. 2003;16(4):376–88.
113. Zaniboni A, Labianca R, Gruppo Italiano per lo Studio e la Cura dei Tumori del D. Adjuvant therapy for stage II colon cancer: an elephant in the living room? Ann Oncol. 2004;15(9):1310–8.
114. Network NCC. Colon cancer version 2.2015. Clinical paractice guidelines in oncology (NCCCN guidelines); 2014 [cited 2014]; Available from: www.nccn.org.
115. Devaud N, Gallinger S. Chemotherapy of MMR-deficient colorectal cancer. Farm Cancer. 2013;12(2):301–6.
116. Minsky BD, Cohen AM, Enker WE, Kelsen DP, Kemeny N, Frankel J. Efficacy of postoperative 5-FU, high-dose leucovorin, and sequential radiation therapy for clinically resectable rectal cancer. Cancer Investig. 1995;13(1):1–7.
117. Minsky BD, Cohen AM, Enker WE, Sigurdson E. Phase I/II trial of pre-operative radiation therapy and coloanal anastomosis in

distal invasive resectable rectal cancer. Int J Radiat Oncol Biol Phys. 1992;23(2):387–92.
118. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med. 2005;340(11):858.
119. Neves GR, Chapchap P, Sredni ST, Viana CR, Mendes WL. Childhood carcinoid tumors: description of a case series in a Brazilian Cancer Center. 2006;124(1):21–5.
120. Spunt SL, Pratt CB, Rao BN. Childhood carcinoid tumors: the St Jude Children's Research Hospital experience. J Pediatr Surg. 2000;35(9):1282–6.
121. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35825 cases in the United States. J Clin Oncol. 2008;26(18):3063.
122. Boxberger N, Redlich A, Boger C, Leuschner I, von Schweinitz D, Dralle H, et al. Neuroendocrine tumors of the appendix in children and adolescents. Pediatr Blood Cancer. 2013;60(1):65–70.
123. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. Ann Surg. 2004;240(1):117.
124. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97:934–59.
125. Williams ED, Sandler M. The classification of carcinoid tumours. Lancet. 1963;1(7275):238.
126. Kvols LK. Metastatic carcinoid tumors and the malignant carcinoid syndrome. Ann N Y Acad Sci. 1994;733:464.
127. Dall'Igna P, Ferrari A, Luzzatto C, Bisogno G, Casanova M, Alaggio R, et al. Carcinoid tumor of the appendix in childhood: the experience of two Italian Institutions. JPGN. 2005;40:216–9.
128. Feldman JM. Carcinoid tumors and syndrome. Semin Oncol. 1987;14(3):237.
129. Çoşkun H, Bostancı O, Dilege ME, et al. Carcinoid tumors of appendix. Treatment and outcome. Ulus Travma Acil Cerrahi Derg. 2006;12:150–4.
130. Anonymous. Neoplasms of the neuroendocrine pancreas. In: Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. WHO classification of tumours of endocrine organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017. p. 209–40.
131. Rindi G, Arnold R, Bosman FT. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman TF, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumors of the digestive system. Lyon: International Agency for Research on Cancer (IARC); 2010. p. 13.
132. Oberg K. Carcinoid tumors: molecular genetics, tumor biology, and update of diagnosis and treatment. Curr Opin Oncol. 2002;14:38–45.
133. Granberg D, Wilander E, Oberg K, Skogseid B. Prognostic markers in patients with typical bronchial carcinoid tumors. J Clin Endocrinol Metab. 2000;85:3425–30.
134. Yachida S, Vakiani E, White CM, Zhong Y, Saunders T, Morgan R, et al. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. Am J Surg Pathol. 2012;36(2):173–84.
135. Howell DL, O'Dorisio MS. Management of neuroendocrine tumors in children, adolescents, and young adults. J Pediatr Hematol Oncol. 2012;34(Suppl 2):S64–8.
136. Shebani KO, Souba WW, Finkelstein DM, Stark PC, Elgadi KM, Tanabe KK, et al. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. Ann Surg. 1999;229(6):815–21; discussion 822–813.
137. Mani S, Modlin IM, Ballantyne G, Ahlman H, West B. Carcinoids of the rectum. J Am Coll Surg. 1994;179(2):231–48.
138. de Mestier L, Brixi H, Gincul R, Ponchon T, Cadiot G. Updating the management of patients with rectal neuroendocrine tumors. Endoscopy. 2013;45(12):1039–46.
139. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology. 2012;95(2):98–119.
140. Cloyd JM, Poultsides GA. Non-functional neuroendocrine tumors of the pancreas: advances in diagnosis and management. World J Gastroenterol. 2015;21(32):9512–25.
141. More J, Young J, Reznik Y, Raverot G, Borson-Chazot F, Rohmer V, et al. Ectopic ACTH syndrome in children and adolescents. J Clin Endocrinol Metab. 2011;96(5):1213–22.
142. Stiller C. Childhood cancer in Britain: incidence, survival and mortality. New York: Oxford University Press Inc; 2007. 104 p.
143. Pappo AS, Janeway K, Laquaglia M, Kim SY. Special considerations in pediatric gastrointestinal tumors. J Surg Oncol. 2011;104(8):928–32.
144. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg. 2000;231(1):51–8.
145. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29(1):52–68.
146. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol. 2006;30(4):477–89.
147. Cypriano MS, Jenkins JJ, Pappo AS, Rao BN, Daw NC. Pediatric gastrointestinal stromal tumors and leiomyosarcoma. Cancer. 2004;101(1):39–50.
148. Pappo AS, Janeway KA. Pediatric gastrointestinal stromal tumors. Hematol Oncol Clin North Am. 2009;23(1):15–34, vii.
149. Benesch M, Leuschner I, Wardelmann E, Thielen M, Schmid I, Kontny U, et al. Gastrointestinal stromal tumours in children and young adults: a clinicopathologic series with long-term follow-up from the database of the Cooperative Weichteilsarkom Studiengruppe (CWS). Eur J Cancer. 2011;47(11):1692–8.
150. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain of function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279:577–80.
151. Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003;299(5607):708.
152. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21:4342–9.
153. Janeway KA, Kim SY, Lodish M, Nose V, Rustin P, Gaal J, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking kit and PDGFRA mutation. Proc Natl Acad Sci U S A. 2010;108(1):314–8.
154. Pantaleo MA, Astolfi A, Indio V, Moore R, Thiessen N, Heinrich MC, et al. SDHA loss of function mutations in kit-PDGFRA wild type gastrointestinal stromal tumors identified by massively parallel sequencing. J Natl Cancer Inst. 2011;103(12):983–7.
155. Burnichon N, Briere JJ, Libe R, Vescovo L, Riviere J, Tissier F, et al. SDHA is a tumor suppressor gene causing paraganglioma. Hum Mol Genet. 2010;19(15):3011–20.
156. Tarn C, Rink L, Merkel E, Flieder D, Pathak H, Koumbi D, et al. Insulin-like growth factor 1 receptor is a potential therapeutic target for gastrointestinal stromal tumors. Proc Natl Acad Sci U S A. 2008;105(24):8387–92.
157. Stratakis CA, Carney JA. The triad of paragangliomas, gastric stromal tumors and pulmonary chondromas (Carney triad), and

the dyad of paragangliomas and gastric stromal sarcomas (Carney-Stratakis syndrome): molecular genetics and clinical implications. J Intern Med. 2009;266(1):43.
158. Maeyama H, Hidaka E, Minami S, Kajiyama M, Kurais A, Mori H, et al. Familial gastrointestinal stromal tumor with hyperpigmentation: association with germline mutation of the c-kit gene. Gastroenterology. 2001;120(1):210.
159. Agaimy A, Markl B, Arnholdt H, Hartmann A, Scheneider-Stock R, Chetty R. Sporadic segmental interstitial cell of Cajal hyperplasia (microscopic GIST) with unusual diffuse longitudinal growth replacing the muscularis propria: differential diagnosis to hereditary gist syndromes. Int J Clin Exp Pathol. 2010;3(5):549–56.
160. Miettinen M, Fetsch JF, Sobin LH, Lasota J. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol. 2006;30(1):90.
161. Mussi C, Schildhaus HU, Gronchi A, Wardelmann E, Hohenberger P. Therapeutic consequences from molecular biology for gastrointestinal stromal tumor patients affected by neurofibromatosis type 1. Clin Cancer Res. 2008;14(14):4550.
162. Wang JH, Lasota J, Miettinen M. Succinate Dehydrogenase Subunit B (SDHB) is expressed in neurofibromatosis 1-associated Gastrointestinal Stromal Tumors (GISTS): implications for the SDHB expression based classification of GISTS. J Cancer. 2011;16(2):90–3.
163. Janeway KA, Pappo A. Treatment guidelines for gastrointestinal stromal tumors in children and young adults. J Pediatr Hematol Oncol. 2012;34(Suppl 2):S69.
164. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23(2):70.
165. Miettinen M, Lasota J, Sobin LH. Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol. 2005;29:1373–81.
166. Agaram NP, Laquaglia MP, Ustun B, Guo T, Wong GC, Socci ND, et al. Molecular characterization of pediatric gastrointestinal stromal tumors. Clin Cancer Res. 2008;14:3204–15.
167. Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era-a population-based study in western Sweden. Cancer. 2005;103:821–9.
168. Fletcher CDM, Berman JJ, Corless CL, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459–65.
169. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39:1411.
170. Watson RR, Binmoeller KF, Hemerski CM, Shergill AK, Shaw RE, Jaffee IM, et al. Yield and performance characteristics of endoscopic ultrasound-guided fine needle aspiration for diagnosing upper GI tract stromal tumors. Dig Dis Sci. 2011;56(6):1757–62.
171. Janeway KA, Pappo AS. Pediatric gastrointestinal stromal tumors. Hematol Oncol Clin North Am. 2009;23:15–34.
172. Champagne MA, Capdeville R, Krailo M, Qu W, Peng B, Rosamilia M, et al. Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. Blood. 2004;104(9):2655–60.

Gastrointestinal Lymphomas

19

Alma Aslan, Serkan Akın, Taner Babacan, and Evren Özdemir

Gastrointestinal Lymphomas

The gastrointestinal (GI) tract is the predominant site of extranodal lymphoma involvement secondary to widespread nodal disease [1], with approximately 5–20% of extranodal lymphomas occurring in the GI tract [2]. Primary non-Hodgkin lymphomas (NHLs) of the GI tract are rare (constituting 1–4% of all GI malignancies) and 90% are of B-cell origin [3, 4], while secondary GI involvement is relatively common.

Primary GI lymphoma may involve any part of the GI tract from the oropharynx to the rectum [5, 6]. The most commonly involved sites are as follows: stomach (60–75%), small intestine (9%), ileocecal region (7%), and colorectal region (<1%).

The criteria for primary gastrointestinal lymphoma have been proposed by Dawson et al. (Table 19.1). Histological subtypes of lymphomas may preferentially involve specific sites in the gastrointestinal tract (Table 19.2). There are several known risk factors for the development of primary GI lymphomas (Table 19.3). Pretreatment work-up and tissue biopsy are necessary for definitive diagnosis and staging of the disease (Table 19.4).

There is limited consensus on the best staging system of primary GI lymphoma, with 3 staging systems in use: Ann-Arbor staging with Musshoff modification, Lugano staging system (incorporating measures of distal nodal involvement), and Paris staging system (a modified tumor-node-metastasis [TNM] staging system).

Treatment depends upon a patient's clinical condition, histological subtype, and stage of the disease and may range from observation to stem cell transplantation.

This chapter will focus on the most common primary GI lymphomas of the stomach, small intestine, and colon, and extranodal involvement of the GI tract by systemic lymphomas. Epidemiology, etiology and risk factors, diagnostic procedures, staging, treatment, and follow-up of GI lymphomas will be discussed in more detail.

Table 19.1 Dawson's criteria for primary GI lymphoma

Absence of peripheral lymphadenopathy at the time of presentation
Lack of mediastinal lymph nodes
Normal total and differential white cell count
Predominance of bowel lesion at the time of laparotomy with only lymph nodes obviously affected in the immediate vicinity
No involvement of liver and spleen

Table 19.2 Histologic subtypes' predilection site

Histologic subtype	Predilection site
Gastric MALT lymphoma (MALTOMA)	Stomach, usually multifocal
Diffuse large B-cell lymphoma	Stomach
Mantle cell lymphoma (MCL)	Terminal ileum, jejunum, colon
Enteropathy-associated T-cell lymphoma (EATL)	Jejunum
Follicular lymphoma	Duodenum, jejunum, ileum, usually multifocal
Burkitt lymphoma	Terminal ileum
Non-IPSID non-gastric MALT lymphoma (Western type)	Duodenum, jejunum
Immunoproliferative small intestinal disease (IPSID)	Duodenum, jejunum

Table 19.3 Risk factors in the pathogenesis of primary GI lymphomas

Bacterial infections	*Helicobacter pylori* *Campylobacter jejuni*
Viral infections	HIV, HBV, HCV, EBV, HTLV-1
Inflammatory bowel disease	Celiac disease Crohn's disease
Immunosuppression	Post-transplant Immunosuppressive agents

HIV human immunodeficiency virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *EBV* Epstein-Barr virus, *HTLV-1* human T-lymphotropic virus type 1

A. Aslan · S. Akın · T. Babacan · E. Özdemir (✉)
Department of Medical Oncology, Hacettepe University Institute of Cancer, Sıhhiye, Ankara, Turkey

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_19

Table 19.4 Pretreatment evaluation of primary gastrointestinal lymphomas

History and physical examination
CBC with differential
Liver and renal function tests with electrolytes, LDH
Serology for human immunodeficiency virus, hepatitis B and C, Epstein-Barr virus
Computed tomography of chest, abdomen and pelvis
FDG-PET in aggressive lymphomas
Endoscopic ultrasound for upper GI lymphomas
Endoscopic biopsies
Laparotomy depending on clinical presentation and accessibility
Tests for *Helicobacter pylori* in gastric lymphoma, *Campylobacter jejuni* in intestinal lymphoma
Molecular markers: t(11;18) for gastric MALT lymphoma, t(11;14) for mantle cell lymphoma, t(14;18) for follicular lymphoma, myc for Burkitt's lymphoma
Bone marrow aspiration and biopsy

CBC complete blood count, *LDH* lactate dehydrogenase, *FDG-PET* fluorodeoxyglucose positron emission tomography, *GI* gastrointestinal, *MALT* mucosa-associated lymphoid tissue

Primary Gastric Lymphomas

Epidemiology

The stomach is the most common extranodal site of lymphoma and accounts for 68–75% of GI lymphomas [7, 8]. Primary gastric lymphoma accounts for 3–5% of gastric neoplasms and is the most common site of primary GI lymphoma [2, 4]. Primary gastric lymphoma can arise from mainly 2 different sources: extranodal marginal B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type and diffuse large B-cell lymphoma. The majority of primary lymphomas of the stomach are MALT type (40–50%), of which 70–80% are confined to the stomach (stage IE). Some studies report that the incidence of primary gastric lymphoma has been increasing during the past decades [9, 10]. Gastric lymphoma reaches its peak incidence between the ages of 50–60 years and is most common in men [11]. The distribution of primary GI lymphomas varies in different geographical regions, as B-cell lymphomas are more frequently reported in Western countries, while Eastern countries have a higher incidence of T-cell lymphomas. This difference might also be due to host factors.

Etiology and Risk Factors

The etiology of gastric lymphoma remains unclear, but associated predisposing factors include *Helicobacter pylori* infection, immunodeficiency (e.g., human immunodeficiency virus [HIV] infection), hepatitis B infection, autoimmune diseases, long-standing immunosuppressive therapy (e.g., post-transplantation), celiac disease (CD), and inflammatory bowel disease (IBD) [12–24].

Helicobacter pylori infections are especially associated with the development of most MALT lymphomas of the stomach (90%). The other sites of the GI tract are affected to a lesser extent. The stomach does not contain significant lymphoid tissue, but lymphoma also can arise from mucosal sites. The development of MALT lymphomas is linked to the clonal expansion of B cells that accompanies chronic gastritis in the presence of *H. pylori*. *H. pylori*-induced gastritis first leads to the accumulation of CD4+ lymphocytes and mature B cells in the gastric lamina propria. Antigens derived from *H. pylori* drive the activation of T cells, B-cell proliferation, and lymphoid follicle formation, which if persistent can evolve into a monoclonal lymphoma. *Helicobacter pylori* plays a role in the development of most MALT lymphomas and may play a similar role in the development of diffuse large B-cell lymphoma (DLBCL). A few studies have shown complete remission after eradication therapy alone [12–24].

Immunodeficiency is defined as a state of impaired function of the immune system that can be congenital, acquired, or iatrogenic. Two conditions mainly determine the occurrence of lymphomas: human immunodeficiency virus (HIV) infection with the associated acquired immunodeficiency syndrome (AIDS) and post-transplant immunosuppression. In both situations, the GI tract is the most involved site. Post-transplant lymphoproliferative disorders can occur late after solid-organ transplantation associated with intensive long-term immunosuppressive therapy to prevent rejection of the transplant [15, 16] . AIDS-related lymphoma can involve any area of GI tract and is mostly associated with advanced disease and low CD4 counts. The rate of GI tract involvement in AIDS-related lymphoma is approximately 14% [17, 18].

An association between IBD and lymphoma has been shown, but the increased risk of lymphoma in patients treated with immunosuppressive agents (e.g., azathioprine, 6-mercaptopurine) or tumor necrosis factor-alpha (TNF-alpha) inhibitors (e.g., etanercept, infliximab) remains controversial [21, 22]. The lymphoma risk in association with anti-TNF agents is also confounded by the strong association between high cumulative disease activity and development of lymphoma [23].

The association between CD and lymphoma has long been established. The most frequent malignancy associated with CD is a high-grade, T-cell NHL of the upper small intestine. Also, CD may be associated with other NHL types of both the B- and T-cell type in either the gut or other primary sites [20, 24].

Diagnosis

Patients with gastric lymphoma typically present with nonspecific symptoms frequently seen with more common gastric conditions, such as peptic ulcer disease, non-ulcer dyspepsia, and gastric adenocarcinoma. The most common presenting symptoms include epigastric pain or discomfort (93%), anorexia, weight loss, nausea and/or vomiting, occult gastrointestinal bleeding, and early satiety. Systemic B symptoms (fever, night sweats) are rarely seen [24, 25]. The duration of symptoms is variable, ranging from a few days to years.

The diagnosis of gastric lymphoma may be suggested by endoscopic and imaging findings, but must be confirmed by histopathological evaluation. The diagnosis of gastric lymphoma is usually established by upper GI endoscopy with biopsy. Laparotomy and laparoscopy are typically reserved for patients with complications such as perforation or obstruction.

Both suspicious-appearing lesions and normal-appearing mucosa must be biopsied because gastric lymphoma can occasionally present as a multifocal disease [13]. Multiple biopsies should be obtained from the stomach, duodenum, and gastroesophageal junction. An endoscopic ultrasound (EUS) should determine the depth of invasion and the presence of perigastric nodes [26, 27].

Endoscopists should aim to attain the largest biopsy specimen possible. Endoscopic ultrasound-guided fine needle aspiration biopsy (FNAB) [28] or endoscopic submucosal resection may provide even greater diagnostic capability.

Findings on upper GI endoscopy may include mucosal erythema, a mass or polypoid lesion with or without ulceration, benign-appearing gastric ulcer, nodularity, or thickened and cerebroid gastric folds [29, 30]. Superficial spreading or diffuse infiltrating lesions on EUS were seen with MALT lymphoma, while mass-forming lesions were typical of diffuse large B-cell lymphoma (DLBCL) [31].

Accurate diagnosis is established by histopathological and immunohistochemical examination, supplemented by cytogenetic and molecular biology tests. A complete diagnosis requires a histopathological classification and a correct staging, both of them having an impact on the therapeutic decision.

The vast majority (greater than 90%) of gastric lymphomas are equally divided into two histological subtypes: MALT lymphoma and DLBCL [7, 8].

MALT lymphoma can be divided into *H. pylori* positive or negative based on the presence of *Helicobacter pylori*. Most patients (>90%) with gastric MALT lymphoma are *H. pylori* positive. *H. pylori* negative MALT lymphoma tends to have a higher frequency for t(11;18) (q21;q21) translocation compared to *H. pylori* positive MALT lymphoma [32, 33].

Extranodal marginal zone B-cell lymphoma (MZL), also called low-grade B-cell lymphoma of mucosa-associated lymphoid tissue, is an extranodal lymphoma that arises in a number of epithelial tissues, including the stomach, salivary gland, lung, small bowel, thyroid, and elsewhere. It was originally referred to as a "pseudo-lymphoma" because of its tendency to remain localized to the tissue of origin for long periods of time, but it is now recognized that it is a clonal B-cell neoplasm that frequently recurs locally and has the potential for systemic spread and transformation to a high-grade B-cell lymphoma. MALT lymphoma comprises up to 50% of all primary lymphomas involving the stomach [12, 24]. Histologically, the most significant finding is the presence of a variable number of lymphoepithelial lesions defined by invasion and partial destruction of mucosal glands by the tumor cells. Extranodal MZL is postulated to arise from post germinal center memory B cells with the capacity to differentiate into marginal zone and plasma cells. The tumor B cells can express the surface immunoglobulin (Ig) and pan-B antigens (CD19, CD20, and CD79a), the marginal zone-associated antigens (CD35 and CD21, and lack CD5, CD10, CD23), and cyclin D1. In normal B and T cells, signals produced by the interaction of antigen with antigen receptors on the cell surface cause the protein B-cell leukemia/lymphoma 10 (BCL-10) to bind to the MALT lymphoma-associated translocation (MALT1) protein. This triggers additional events that result in the activation of nuclear factor kappa B (NF-κB), a transcription factor that turns on a set of genes that promote B-cell survival [34]. The most commonly seen translocations are t(11;18) (q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32), and t(3;14)(p13;q32). Specifically, the t(11;18) translocation fuses the apoptosis inhibitor-2 gene on chromosome 11 (variously called API2 or IAP2) with the MALT1 gene on chromosome 18 [35]. These result in overexpression of BCL-10, which causes cellular transformation and provides a survival advantage to the neoplastic B cells. Nuclear expression of BCL-10 or NF-κ(kappa)B in gastric MALT, determined by immunohistochemistry, is associated with resistance of gastric MZLs to antibiotic therapy, even in those tumors that lack the t(11;18) [36].

The diagnosis of extranodal MZL is based upon morphologic, immunophenotypic, and genetic analyses of tissue taken from an affected site. As previously described in more detail, the morphological review reveals a polymorphous infiltrate of small cells with reactive follicles. While large cells are typically present, they are by definition the minority. On immunophenotyping, cells are positive for B-cell markers CD19, CD20, and CD22 and negative for CD5, CD10, and CD23. Molecular diagnostic analysis consisting of polymerase chain reaction (PCR)-based analysis of IgH gene rearrangements can also be very helpful in distinguishing extranodal MZL from reactive proliferations. Chromosomal abnormalities, usually t(11;18), is found in almost all cases and can be diagnostically helpful.

DLBCLs are a heterogeneous group of tumors that are clinically, histologically, immunophenotypically, and cytogenetically variable. They can be divided into four subgroups, (1) T-cell histiocyte-rich large B-cell lymphoma, (2) intravascular lymphoma, (3) lymphomatoid granulomatosis, and (4) primary mediastinal DLBCL, according to the gene expression patterns with each having a different outcome. Gastrointestinal DLBCL includes lesions previously called high-grade MALT lymphoma. It can occur anywhere along the GI tract and is the most common histology for primary gastric lymphoma, representing approximately 50% of cases. Compared with patients with low-grade MALT lymphoma, these patients tend to have more systemic symptoms, a more advanced stage at diagnosis, and a worse prognosis. At endoscopy, most DLBCLs appear as infiltrating lesions with bizarre ulcerations or conspicuous fold enlargements. In some patients, there is a peculiar polypoid nodularity of the invaded segment. These alterations can appear as single or multiple findings. The most commonly seen translocations as mentioned earlier include t(14;18)(q32;q21) with BCL2-rearrangement, t(3;14) (p27;q32) with BCL6-rearrangement, and t(8;14) (q24;q32) with MYC rearrangement, respectively. Variability has been observed in CD45, CD5, and CD10 expression, with the CD10 expression in particular considered as a prognostic indicator [37]. MYC, an oncogenic transcription factor, is recognized as one of the most frequently altered genes in human malignancies. MYC is also a critical player during lymphoma development [38]. BCL-2, an anti-apoptotic gene, has been implicated in conferring chemotherapy resistance in non-Hodgkin's lymphoma and has been extensively studied as a prognostic biomarker in DLBCL [39]. MYC translocations, with or without BCL-2 translocations, have been associated with inferior prognosis in DLBCL. DLBCL patients with both MYC and BCL-2 protein co-expression have shown inferior overall survival and progression-free survival [40].

The remaining cases of gastric lymphoma may represent any histology, but the most commonly seen are mantle cell lymphoma, follicular lymphoma, and peripheral T-cell lymphoma [7, 8].

After a diagnosis of GI lymphoma is confirmed, a pretreatment evaluation determines the extent of the disease. Laboratory studies include a complete blood count with differential, HIV serology, chemistries with liver and renal function, electrolytes, lactate dehydrogenase (LDH), and serological testing for hepatitis B and hepatitis C.

A contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis should be performed to evaluate for distant disease. The use of positron emission tomography (PET) is controversial except in cases of DLBCL [41]. Patients should be tested for *H. pylori*, which can be detected by histological specimen, biopsy urease test, urea breath test, stool antigen test, or serology. In addition, fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) testing for t(11;18) should be performed. Bone marrow biopsy and aspirate should be performed on all patients. Men and women with childbearing potential should receive counseling about the potential effect of treatment on their fertility and options for fertility-preserving measures, and women of childbearing should undergo a pregnancy test if chemotherapy is planned.

Staging

A proper staging for GI lymphomas will include [42]:

1. *Physical examination*: evaluation of superficial lymph nodes; abdomen palpation to detect liver enlargement, splenomegaly, and abdominal masses.
2. *Endoscopic ultrasonography*, which is the gold standard in defining the locoregional GI involvement.
3. *Computed tomography* of the neck, chest, and abdomen in order to detect involvement of nodes above and below the diaphragm and also other extranodal involvement not pertaining to the GI tract.
4. *Positron emission tomography* is not generally indicated as a staging procedure, especially in MALT lymphomas, but it retains a role in defining the pretreatment lymphomatous involvement and response to treatment.
5. *Bone marrow biopsy*: notwithstanding the low-grade, indolent diseases that tend to remain localized at the GI tract, bone marrow biopsy should be performed in order to exclude a marrow involvement that could influence treatment and follow-up management. However, the level of evidence on its utility is poor [43].

Several staging systems have been developed over the past decades to improve prognostic stratification of primary GI lymphoma, mainly taking into account different clinical parameters. The most popular staging system is the Ann Arbor system. The spreading patterns of extranodal lymphomas are different from primary nodal lymphomas. Because of this, the use of Ann Arbor staging is not suitable, especially for primary gastric lymphomas. Several adaptations and modifications have been done for gastrointestinal lymphomas by Musshoff (Table 19.5) [44]. The Lugano staging system is a modification of the original Ann Arbor staging system designed for the staging of primary gastrointestinal lymphomas. It was developed to incorporate measures of depth of invasion and distant nodal involvement (Table 19.6) [45]. Early (stage I/II) disease includes a single primary lesion or multiple, noncontiguous lesions confined to the GI tract that may have nodal involvement. There is no stage III in the Lugano system. Advanced (stage IV) disease displays

Table 19.5 Ann Arbor lymphoma staging system, modified by Musshoff, for extranodal lymphomas

Stage of disease	Extent of disease
Stage I	Single lymphatic organ or extranodal site
Stage II	Two or more lymphatic regions on the same side of the diaphragm, or a single extranodal organ plus lymph node involvement on the same side of the diaphragm
Stage II1	Regional lymph nodes involved
Stage II2	Distant lymph node involvement
Stage III	Lymph node involvement detected on both sides of the diaphragm
Stage IV	Disseminated disease with involvement of other extranodal sites (i.e., liver, bone marrow, abdominal wall)

Table 19.6 Lugano system for staging of gastrointestinal lymphomas

Stage of disease	Extent of disease
Stage I	Tumor confined to the GI tract, single primary site or multiple noncontinuous lesions
Stage I1	Tumor does not exceed the mucosa and submucosa
Stage I2	Tumor infiltrates into muscularis propria and/or subserosa and/or serosa
Stage II	Tumor extends into abdomen from primary GI site
Stage II1	Local lymph node involvement
Stage II2	Distant lymph node involvement
Stage IIE	Penetration of serosa with involvement of adjacent organs/tissues
Stage IV	Disseminated disease with involvement of extranodal sites, or primary GI lesion plus supradiaphragmatic nodal involvement

GI gastrointestinal

disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement. A modified TNM staging system, also called the Paris staging system, suggested by European Gastro-Intestinal Lymphoma Study Group modeled after the staging of gastric adenocarcinoma, is not as commonly used (Table 19.7) [46]. Treatment decisions are made according to these staging systems.

Treatment and Prognostic Factors

Gastric lymphoma has better prognosis than intestinal lymphoma and gastric adenocarcinoma, perhaps because of the tendency of gastric lymphomas to remain localized in the stomach for a long time. The stage and histological grade of the disease are the most important independent prognostic factors. In fact, depth of the invasion of the wall and size of the tumor and serosal penetration are other negative prognostic factors [47]. DLBCL with *MYC* and *BCL-2* translocations have been associated with a poor prognosis and worse chemotherapy response [48]. Other negative survival factors described in the literature are older age, T-cell lymphoma,

Table 19.7 Paris staging system (TNMB) for primary gastrointestinal tract lymphomas

Stage of disease	Extent of disease
Tx	Lymphoma extent unspecified
T0	No evidence of lymphoma
T1	Lymphoma confined to the mucosa/submucosa
T1m	Lymphoma confined to the mucosa
T1sm	Lymphoma confined to the submucosa
T2	Lymphoma infiltrates muscularis propria or subserosa
T3	Lymphoma penetrates serosa without invading adjacent structures
T4	Lymphoma infiltrates adjacent structures or organs
Nx	Nodal involvement not assessed
N0	No evidence of lymph node involvement
N1	Involvement of regional lymph nodes (for GL: perigastric nodes, as well as those located along the splenic, the common hepatic and the left gastric arteries)
N2	Involvement of intra-abdominal lymph nodes beyond the regional area
N3	Involvement of extra-abdominal nodes
Mx	Dissemination not assessed
M0	No evidence of extranodal dissemination
M1	Noncontinuous involvement of separate sites in the GI tract (i.e., stomach and rectum)
M2	Noncontinuous involvement of other tissues or organs
Bx	Involvement of bone marrow not assessed
B0	No evidence of bone marrow involvement
B1	Lymphomatous infiltration of the bone marrow

nodular type, elevated lactate dehydrogenase (LDH), lesions with a higher cell proliferation index measured by monoclonal antibody Ki67 or MIB1, and aneuploid lymphoma.

The modalities of treatment for gastric lymphomas have been a controversial subject, and the best regimen has not been standardized. The treatment of gastric MALT lymphoma is dependent on the presence or absence of a concomitant *H. pylori* infection. For early stage (I/II) gastric MALT lymphoma with *H. pylori* infection, *H. pylori* eradication is the initial therapy. It is reported that more than 70% of patients can achieve remission after a successful *H. pylori* eradication [49]. After initial therapy, patients must be monitored with serial endoscopies to evaluate for disease response and recurrence. Tumors demonstrating the t(11;18) translocation are unlikely to respond to *H. pylori* eradication and are candidates for alternative therapies [50]. Patients initially treated with *H. pylori* eradication therapy need to be evaluated after the completion of treatment to determine whether the *H. pylori* was successfully eradicated and whether there has been a tumor response. Approximately 20–30% of patients do not respond to *H. pylori* eradication therapy or demonstrate relapse during follow-up. These patients should be reviewed carefully to confirm the presence of MALT lymphoma and to exclude more aggressive lymphomas [51]. These patients should also be treated with radiotherapy (RT) with a curative

intent. Patients treated with RT almost always attain a complete response (CR) and have lower relapse rates, but have a potential for more complications.

Patients without evidence of *H. pylori* infection, *H. pylori* eradication therapy failures, and those with tumors that demonstrate the t(11;18) translocation are typically treated with local radiation therapy. Other treatments, including immunotherapy, chemoimmunotherapy, and multiagent chemotherapy, are reserved for patients failing or recurring after RT. Single-agent immunotherapy drug rituximab is chimeric mouse anti-human CD20 monoclonal antibody specific for B-cell surface antigen CD20. It has been demonstrated to be effective in MALT lymphoma arising in different extranodal organs including the stomach. The first phase 2 prospective study was conducted by the International Extranodal Lymphoma Group (IELSG) on gastric lymphoma at different disease stages; the overall response rate was 64% [52]. Another larger study evaluated the efficacy of rituximab on resistant/refractory primary gastric lymphoma including patients with t(11;18) (q21;q21); it demonstrated higher response at early stages of disease than those in advanced stages [53]. The addition of rituximab to anthracycline-based combination therapy was evaluated in a small retrospective study that included relapsed MALT lymphoma treated with rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisolone). All patients achieved a complete response [54].

For patients who have early-stage *H. pylori*-negative gastric MALT lymphoma or those with t(11;18), initial treatment with local RT is associated with more long-term remissions.

Patients with advanced stage (Lugano IV) disease are treated with *H. pylori* eradication therapy if they are *H. pylori* positive and then generally observed until the development of symptoms, at which time they undergo treatment with immunotherapy and/or chemotherapy. For asymptomatic patients, an initial observation rather than chemotherapy is suggested. Immunotherapy-based treatment is reserved for disease progression or development of symptoms.

Treatment options that were evaluated in gastric DLBCL include surgery, radiation therapy, chemoimmunotherapy, *H. pylori* eradication therapy, and combinations of the above. In general, most patients are treated with combination chemoimmunotherapy regimen. A few patients may be candidates for a trial of *H. pylori* eradication therapy. *H. pylori* eradication is necessary for a patient with gastric DLBCL because the existence of the bacterium might increase the risk of relapse [55]. Chemotherapy is more tolerable than surgery. For most patients with gastric DLBCL, it is recommended to use combination chemotherapy with rituximab with or without involved-field RT. The use of *H. pylori* eradication therapy alone for limited-stage gastric DLBCL is not universally accepted and requires very close monitoring. Gastric resection is reserved for patients with complications such as perforation or obstruction or intractable bleeding.

Follow-Up

Good clinical judgment, a careful history, and physical examination are the cornerstones of patient follow-up. Patients initially treated with *H. pylori* eradication therapy need to be evaluated 4–8 weeks after the completion of treatment to determine whether the *H. pylori* was successfully eradicated and whether there has been a tumor response. Urea breath testing should be performed to confirm eradication of infection. After successful eradication of *H. pylori*, patients should undergo periodic upper endoscopy with multiple biopsies to evaluate for tumor response and monitor for relapse. Histological evaluation of repeat biopsies remains an essential follow-up procedure to exclude either the possibility of persistent significant disease or, particularly in patients with persistent *H. pylori* infection, the appearance of early epithelial changes, which may be related to gastric carcinoma.

Unfortunately, the interpretation of lymphoid infiltrate in post-treatment gastric biopsies can be very difficult and there are no uniform criteria for the definition of histological remission. We can use the Wotherspoon histological index originally devised to differentiate between gastritis and MALT lymphoma at the time of diagnosis [56]. Using these criteria, patients who demonstrate grade 0–2 lesions are considered to have a histological CR, while grade 3 lesions are classified as a partial response (PR). In contrast, the Gela score defines a histological CR as a normal or empty lamina propria and/or fibrosis with absent or sparse plasmacytes and lymphoid cells in the lamina propria without lymphoepithelial lesions [57]. Following the completion of therapy, patients are seen at periodic intervals to monitor for treatment complications and assess for possible relapse or progression. The frequency and extent of these visits depend upon the comfort of both the patient and physician. There have been no prospective, randomized trials comparing various schedules of follow-up. Following the documentation of the achieved *H. pylori* eradication, a strict endoscopic follow-up is recommended, with multiple biopsies taken 2–3 months after treatment to rule out tumor progression, and subsequently (twice per year for 2 years) to monitor the histological regression of the lymphoma [58, 59].

Because of recurrences in all lymphomas, monitoring is necessary. A long-term careful endoscopic and systemic follow-up (clinical examination, blood counts and minimal

adequate radiological or ultrasound examinations every 12–18 months) is recommended for all patients [59].

Primary Small Intestinal Lymphomas

Malignancies of the small intestine constitute less than 3% of all gastrointestinal malignancies [60]. Lymphoma may occur as primarily in the intestine or more commonly as a component of systemic disease with intestinal involvement. Primary small intestinal lymphoma is defined as an extranodal lymphoma arising in the small bowel with the bulk of disease localized to this site. Contiguous lymph node involvement and distant spread may be seen, but the primary clinical presentation is the small intestine in this situation. Complete blood count and peripheral blood smear must be normal and without any lymphomatous involvement of liver or spleen to diagnose primary intestinal lymphoma as defined by Dawson [5].

Lymphomas of the small intestine account for 20% of all small intestinal malignancies. Approximately 30% of GI lymphomas occur in the small intestine. Lymphomas of the small intestine are most commonly seen in the ileum (65%), followed by the jejunum (25%), and the duodenum (10%). Sometimes involvement of multiple sites may exist [61]. Small intestinal lymphomas are classified as B cell or T cell and low or high grade. The World Health Organization (WHO) classification system determines treatment based on these criteria. Most small intestinal lymphomas are of B-cell origin and non-Hodgkin's lymphomas. Whereas lymphomas of T-cell origin constitute only 20%; and Hodgkin lymphomas of the gastrointestinal tract, either primary or secondary, are extremely rare [62]. Small intestinal lymphomas are mainly divided into three groups: MALT lymphomas, other B-cell lymphomas except MALT lymphoma (e.g., diffuse large B-cell lymphoma, mantle cell lymphoma, Burkitt's lymphoma, follicular lymphoma, etc.), and T-cell lymphomas. MALT lymphomas are also subdivided into two groups: immunoproliferative small intestinal disease (IPSID) and non-IPSID MALT lymphomas. There are two main types of T-cell intestinal lymphomas: enteropathy-associated T-cell lymphoma (EATL) and extranodal NK-/T-cell lymphoma.

Submucosal lymphoid tissue is the origin of lymphoma. Approximately 70% of lymphomas present with bulky tumors that are larger than 5 cm in diameter. The development of a localized or nodular mass that narrows the lumen results in abdominal pain, as well as weight loss, anorexia, vomiting, intestinal obstruction, and, less commonly, gastrointestinal bleeding. Presentation is often marked by perforation. Risk of perforation is related to location of the tumor, with the highest risk being for ileal tumors [7]. B symptoms are uncommon in gastrointestinal lymphomas. Typical presentation of IPSID includes chronic diarrhea and steatorrhea associated with vomiting and abdominal cramps; clubbing of the digits may be observed in physical examination.

Epidemiology

Distribution of lymphoma subtypes is projected by etiological factors and host response to these factors. Although in the Western world small intestinal lymphoma is rare, it is the most common lymphoma in some regions of the world such as Middle East and Mediterranean countries. The age of presentation varies with the histological subtype. Population-based studies show that histology also differs in different parts of the world. All of the small intestinal lymphomas have a slight male predominance.

In contrast to lymphomas involving the stomach, primary small intestinal lymphomas are uncommon in Western countries. MALT lymphomas are the most frequent lymphomas of the small intestine. A distinct form of MALT lymphoma, IPSID, also called Mediterranean lymphoma or alpha-heavy chain disease, diffusely involves the small intestine and was first described in oriental Jews and Arabs. IPSID is seen predominantly in the Middle East and Mediterranean areas, but it may be seen outside these regions. In Middle East and Mediterranean countries, IPSID accounts for 75% of all primary gastrointestinal lymphomas. There is a male predominance with a median age at presentation of 25 years [63]. However, non-IPSID MALT lymphomas are most common in developed countries and they occur in middle-aged men.

The endemic form of Burkett's lymphoma (BL) is approximately 50-fold higher in Africa than other regions of the world. It typically presents in the jaw and is strongly associated with Epstein-Barr virus (EBV). The classic GI presentation, which is an obstructing lesion in the terminal ileum, is primarily seen in sporadic forms of BL or in endemic regions other than Africa. For example, in the Middle East, primary gastrointestinal BL is a common disease of children and it is not associated with EBV. Burkett's lymphoma is also seen in the setting of HIV infection when it often involves the gastrointestinal tract secondarily [64].

Intestinal T-cell lymphoma (ITL) is rare, accounting for approximately 5% of all gastrointestinal lymphomas, and is closely linked with celiac disease. In some regions where celiac sprue has high incidence, EATL could also have high incidence, which reflects marked geographic variation. EATL is most commonly found in adult males with a median age at diagnosis in the sixth decade [65]. However, a small series of Mexican patients with EATL had a median age of 24 years, in whom EBV might be responsible for the disease [66].

Etiology and Risk Factors

In contrast to the well-established relationship between *Helicobacter pylori* and gastric MALT lymphoma, no clear association between small intestinal MALT lymphoma and infectious microorganisms has been identified. *H. pylori* may also cause lymphoma of other GI sites other than the stomach; however, there are controversial data about this association. Low socioeconomic status and poor sanitation, as well as *Campylobacter* infection, are risk factors for IPSID. The close association was confirmed in a retrospective analysis [67]. HLA-Aw19, −B12, −A9 haplotypes are some well-known genetic alleles associated with IPSID [68]. IPSID may be related to bacterial infection, as antibiotic benefit in early stages of disease suggests possible infectious etiology. However, there is not conclusive proof for the pathogenic role of *Campylobacter jejuni* in IPSID.

Chronic inflammation predisposes to 2 of the small intestinal malignancies: adenocarcinoma and lymphoma. There is a small absolute increase in the incidence of intestinal lymphoma among patients with chronic inflammatory bowel disease, especially those receiving immunosuppressive agents. The majority of these lymphomas are of B-cell origin, and many demonstrate infection with EBV. Crohn's disease is more often implicated in the development of lymphoma in the small intestine, while ulcerative colitis is associated with lymphomas of the colorectal region [69]. Another chronic inflammation associated with lymphoma is celiac disease. Patients with celiac disease are at increased risk of EATL, possibly due to the chronic mucosal inflammatory response following gliadin exposure. For 30 years with celiac has approximately a 5% risk of EATL. Patients with celiac who are untreated and diagnosed at an older age have greater risk for EATL [70]. Ulcerative enteritis, which is a feasible variant of EATL, is also a sequela of long-standing celiac disease. Besides the association of celiac and EATL, extranodal NK-/T-cell lymphoma involving the gastrointestinal system might also be closely linked to EBV. Although pathogenesis is not known, EBV is uniformly present in these lymphomas [71].

An increased incidence of lymphoma has been associated with both acquired and congenital immunodeficiency states. Patients with HIV infection have a higher risk of developing intestinal lymphoma due to hyperactivation of B cells. HIV-related lymphomas are generally high-grade B-cell lymphomas with poor prognosis. Generally, secondary involvement of the GI tract may be seen in HIV; however, primary lymphomas of the small intestine have also been reported. Due to immunosuppressive agents for autoimmune disorders and for solid organ transplantation (post-transplantation), patients may have susceptibility to intestinal lymphoma, especially EBV-associated B-cell lymphomas. In general, lymphomas associated with immunodeficiency show a predilection for extranodal sites, particularly the gastrointestinal tract, irrespective of the cause of the immunodeficiency [72]. Congenital or acquired immunodeficiency disorders are not associated with intestinal T-cell lymphoma.

Nodular lymphoid hyperplasia, also called follicular lymphoid hyperplasia, is a benign condition that has been suggested as a potential risk factor for primary small intestinal lymphomas. In childhood, it is usually a benign condition and it usually regresses spontaneously, however, it is related to immunodeficiency and giardiasis in adults. There is conflicting data about responsibility of disease development. Moreover, evidence is stronger for an association of nodular lymphoid hyperplasia with intestinal lymphoma in the absence of immunodeficiency [73]. Previous radiation therapy to the abdomen is also another risk factor for lymphoma as other cancers.

Diagnosis

The diagnosis of small bowel lymphoma has improved over the years. In addition to radiographic techniques such as barium radiography, CT scan, and enterography, endoscopic techniques such as duodenoscopy, balloon-assisted endoscopy, and wireless capsule endoscopy may also be helpful to locate lymphoma in the small intestine. Less invasive techniques such as enterography performed in conjunction with CT or MRI are promising techniques to detect small bowel malignancies. PET is often used in intestinal lymphomas for staging and treatment response assessment, and to restage the disease at the time of recurrence. There is no established imaging method for intestinal lymphoma and any of these methods would be recommended depending on the clinical scenario.

Gastrointestinal lymphoma is often suspected on the basis of characteristic imaging. Suspicious appearance of patterns on contrast radiographs are infiltration and thickening of mucosal folds, mucosal nodules, areas of irregular ulceration, or stasis of contrast material [74]. CT scans of the chest and abdomen are usually the initial diagnostic modalities performed. CT may reveal thickened bowel wall and this finding necessitates further evaluation and biopsy. The value of PET in small intestinal lymphoma depends on histological subtype as for lymphomas elsewhere. For example, lymphomas with aggressive histology such as DLBCL, MCL, BL, and EATL are typically FDG avid. On the other hand, marginal zone lymphomas (i.e., MALT lymphomas) and FL have variable FDG avidity [75]. Importantly, interpretation of FDG avidity in the gastrointestinal tract may be complicated by the presence of physiologic FDG activity or activity related to inflammatory conditions such as Crohn's disease or infections [76]. Incorporation of PET imaging into the pretreatment evaluation of patients with DLBCL, MCL, BL, and EATL of the GI tract has become standard.

Although technically challenging, endoscopic evaluation of the small bowel with biopsy of lesions can be diagnostic as other small bowel malignancies. Endoscopic approaches depend upon the site of involvement. Proximal duodenum may easily be reached with upper endoscopy. Lymphomas of the small intestine may also be accessed by push enteroscopy, while lesions in the distal small bowel may be assessed with intubation of the terminal ileum during colonoscopy. Wireless capsule endoscopy is another useful technique for evaluating the small bowel in patients with suggestive clinical presentations or suspicious radiographic findings. Unlike other endoscopic approaches, capsule endoscopy does not permit tissue sampling.

Besides obtaining tissue, endoscopic findings and location of tumors may guide diagnosis. Different histological variants of lymphoma present with typical findings on endoscopic evaluation. Small nodular or polypoid tumors entirely with or without normal intervening mucosa, referred to as multiple lymphomatous polyposis, may be seen in MCL [77]. Moreover in FL, the most common presentation of endoscopy is multiple smaller polypoid lesions than in MCL, usually in the descending part of the duodenum, with some cases demonstrating clustering around the ampulla of Vater and causing jaundice. In approximately 15% of follicular lymphomas there is a solitary lesion mimicking an adenoma [78]. Large circumferential jejunal ulcers without overt tumor masses are seen in EATL. Biopsies of the involved mucosa demonstrate lymphoma, while biopsies of the normal-appearing mucosa usually show villous atrophy characteristic of celiac disease [79]. Relative predilection sites have been noticed for certain histological subtypes; MCL in terminal ileum and jejunum, EATL in jejunum, FL in duodenum. MALT lymphoma, and FL may be multifocal. In FL, other segments of the small bowel are involved in approximately 17% of cases [80]. DLBCL of the small intestine usually occurs in the ileocecal region. Terminal ileum is the most common site of involvement of primary intestinal BL.

Occasionally, tissue sampling may be very challenging in the small intestine. Intestinal lymphoma can occasionally be diagnosed by intestinal mucosal biopsy derived endoscopically, but since the disease mainly involves the lamina propria, full-thickness surgical biopsies are usually required, such with acute presentations for obstruction, perforation, or major bleeding or patients requiring laparotomy and resection of the involved bowel. At times, surgical exploration and resection of visibly involved segments of bowel may be undertaken if there is a diagnostic dilemma.

Laboratory studies such as complete blood count, serum biochemistry, and serological tests for HIV and hepatitis B and C should be performed initially. Up to 70% of patients with IPSID have alpha heavy chain paraproteinemia [81]. The paraproteinemia may decrease as IPSID progresses from an early stage to advanced lymphoma.

Clinical findings with endoscopic appearance may not be specific. Therefore, pathological confirmation is necessary in almost all gastrointestinal lymphomas. Therapeutic decisions can be made after pathological confirmation. The diagnosis and typing of small intestinal lymphoma depends on careful pathological review of the tissue samples. Immunohistochemistry (IHC) and molecular studies can yield a specific subtype of GI lymphoma. Initial evaluation should identify the cell of origin. IHC and cytometric studies for cell surface antigens differentiate lymphomas as being of either B-cell or T-cell origin. Classically, B-cell lymphomas express CD19, CD20, and CD22, whereas T-cell lymphomas express CD3. Unlike MALT lymphomas of the stomach, IPSID or non-IPSID MALT lymphoma of the small intestine do not harbor a specific chromosomal aberration. As in other MCLs, primary MCL of the small intestine is characterized by the same chromosomal translocation: t(11;14)(q13;q32). BL also harbors cytogenetic abnormalities associated with *myc*. Various tests such as immunophenotyping, flow cytometry, and fluorescence in situ hybridization may be carried out to specify different types of lymphoma. The pathological diagnosis of T-cell lymphomas is based on the combination of histological and immunophenotypical findings such as T-cell clonality and some evidence of celiac disease. Extranodal NK-/T-cell lymphoma usually presents with a facial mass, but primary intestinal type may be also seen. Demonstration of NK-/T-cell markers such as CD2, CD3, and CD56 and EBV are key diagnostic features. EBV-DNA level is also useful to indicate treatment response and recurrence [82].

Staging

The initial staging tools include endoscopy and cross-sectional imaging. Basic laboratory studies and bone marrow biopsy are required as in other lymphomas. Unlike gastric lymphomas, endoscopic ultrasound is rarely used in intestinal lymphomas to evaluate the depth of mucosal infiltration and regional nodal disease.

The Ann Arbor staging system is commonly used for staging of NHL. The spreading patterns of extranodal lymphomas are different from primary nodal lymphomas. The Ann Arbor staging system is considered inadequate for the staging of extranodal lymphomas resulting in several adaptations and modifications for gastrointestinal lymphomas such as the Musshoff modification for extranodal lymphomas [44]. The Lugano staging system was developed to incorporate both depth of invasion and spread of disease. Stage I/II disease includes a single primary lesion or multiple, noncontiguous lesions confined to the GI tract that may have nodal involvement. There is no stage III in the Lugano system. Advanced (stage IV) disease displays disseminated

Table 19.8 Comparison of Lugano classification, modified Ann Arbor staging (Musshoff modification), and Paris staging systems

Stage	Lugano classification	Modified Ann Arbor staging	Paris staging system	Extent of disease
Stage I	I	IE1	T1 N0 M0–1 B0	Mucosa, submucosa
		IE2	T2 N0 M0–1 B0	Muscularis propria, subserosa
		IE2	T3 N0 M0–1 B0	Serosa penetration
Stage II	II1	IIE1	T1–4 N1 M0–1 B0	Regional lymph nodes
	II2	IIE2	T1–4 N2 M0–1 B0	Intra-abdominal distant lymph nodes
	IIE	IE2	T1–4 N0 M0–1 B0	Invasion of adjacent organ
Stage IV	IV	IIE	T1–4 N3 M0–1 B0	Extra-abdominal lymph nodes
		IVE	T1–4 N0–2 M2 B0	Diffuse/disseminated spread
		IVE	T1–4 N0–2 M0–1B1	Bone marrow infiltration

extranodal involvement or concomitant supra-diaphragmatic nodal involvement [45]. However, it may cause more confusion than benefit. The European Gastro-Intestinal Lymphoma Study Group (EGILS) proposed a modified TNM staging system, the Paris staging system [46]. However, there are some conflicts within these staging systems. For example, the Musshoff modification system does not take into account direct spread into adjacent tissues or organs, which would be stage IIE in the Lugano system. Also, the Paris M1 stage indicates discontinuous involvement of separate sites in the gastrointestinal tract (e.g., rectum and duodenum) and is not represented in either Musshoff modification or Lugano classification. The Modified Ann Arbor staging system, Lugano classification, and Paris staging systems are the most common staging tools in gastrointestinal lymphomas. A comparison of them is summarized in Table 19.8.

Treatment

Treatment for lymphoma of the small intestine depends on the subtype and stage of the cancer. There is a wide therapeutic range of watch and wait, antibiotics, chemotherapy, immunotherapy, radiation, and surgery, including combinations of different modalities, in treating small intestinal lymphomas. Unlike most other small bowel tumors, the mainstay of treatment is chemotherapy with or without radiotherapy, and resection should generally be avoided. Emergent surgical intervention will be required for bleeding or perforation. Small intestinal lymphoma sometimes requires laparotomy for establishing diagnosis and for treatment. Low-grade lymphomas may be cured solely by resection. Some studies have revealed the benefit for adjuvant chemotherapy after surgery [83]. The benefit of chemotherapy in B-cell lymphomas is more than that in T-cell lymphomas. Radiotherapy may have some benefit in duodenal lymphomas, however, multifocality and its spread make it challenging [84]. Choice of chemotherapy depends on the histology of aggressive lymphoma. Prognosis of small intestinal lymphoma depends on histological subtype, histological grade of differentiation, stage of disease, and International Prognostic Index (IPI) [85]. Low-grade B-cell lymphomas have the best chance of survival, whereas T-cell lymphomas have the worst [7]. Treatment of small intestinal lymphomas according to histological subtype is described as follows.

Optimal treatment of IPSID is not established yet because there are few studies in this lymphoma. Earlier stages are treated with antibiotics, with the addition of chemotherapy and radiation for later stages. The use of antibiotics against *H. pylori* and *C. jejuni* may result in regression of early stage IPSID that is confined to the intestinal mucosa. Culture results may guide antibiotic preference. If cultures do not yield any growth then ampicillin, metronidazole, or tetracycline should be used. However, most patients relapse with high-grade disease, and radiotherapy and/or chemotherapy as well as nutritional support is the mainstay of treatment [86]. Addition of tetracycline to anthracycline-based chemotherapeutic regimens achieves a 5-year survival rate of up to 70% in cases of advanced stage and recurrent disease [87]. The chemotherapy regimen used in IPSID-type MALT lymphoma of the small intestine includes cyclophosphamide, vincristine, doxorubicin, and prednisone with adding rituximab (R-CHOP).

Indolent lymphomas of the small intestine include some forms of non-IPSID MALT lymphoma and follicular lymphoma. Stage of the non-IPSID MALT lymphoma determines treatment modality. Early stage of disease should be treated with local therapy using surgery or radiotherapy [88]. Treatments of patients with non-IPSID MALT lymphoma accompanying high-grade histology (e.g., DLBCL) have to be aggressive as in the gastric counterpart. Isolated MALT lymphomas are categorized as indolent lymphomas, so treatment may be similar to other indolent forms such as follicular lymphoma (FL). Primary intestinal follicular lymphoma is a diffuse indolent disease that has been successfully treated with a variety of modalities: watch and wait, radiation, rituximab, and chemotherapy. There is no information about using antibiotics in non-IPSID MALT lymphoma of the intestine.

Due to small sample sized studies of intestinal DLBCL, optimal treatment has not been identified. Although there has been no randomized clinical trial, combination regimens

including agents such as R-CHOP may improve outcomes in intestinal DLBCL. Surgery is reserved for complications such as perforation, obstruction, bleeding, or large inflammatory mass. After surgical resection, adjuvant usage of combinations such as R-CHOP may also provide benefit [89]. In the absence of prospective randomized trials, surgery plus chemotherapy appears to produce better outcomes than chemotherapy alone [83]. There is no role of radiotherapy in the treatment of small intestinal DLBCL because of the risks for intestinal radiation [84].

The other aggressive B-cell lymphomas MCL and BL are treated with chemotherapy initially [90]. Rarity of these diseases does not allow major clinical trials, and the treatment of these lymphomas is similar to their nodal forms. Induction and consolidation regimens should be used and autologous hematopoietic cell transplantation (HCT) should be considered in appropriate patients. In some cases surgery and radiotherapy might also be considered.

Treatment of intestinal T-cell lymphomas, either EATL or extranodal NK-/T-cell lymphoma, must be aggressive. Historical data with standard CHOP show poor response in all T-cell lymphomas. Based on these unsatisfactory outcomes in extranodal NK-/T-cell lymphomas, a novel regimen called SMILE (steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) was developed. This regimen consists of methotrexate 2 g/m^2 on day 1; ifosfamide 1500 mg/m^2, etoposide 100 mg/m^2, and dexamethasone 40 mg/body from days 2 to 4; and L-asparaginase a total of 7 doses 6000 U/m^2 every other day from day 8 to day 20. SMILE appears to be more effective than CHOP [91]. Surgery has a limited role unless there is a local complication of the disease. Patients with EATL who may have malnutrition will experience difficulties in wound healing and infection. Enteropathy-associated T-cell disease is treated with combination chemotherapy like other high-grade T-cell lymphomas. Particularly in patients younger than 60 years, the addition of etoposide to CHOP was found to be superior to CHOP alone in patients with peripheral T-cell lymphoma [92]. During the first remission, autologous HCT should be considered in patients with EATL. More recently, a promising regimen of IVE/MTX (ifosfamide, vincristine, etoposide/methotrexate) followed by autologous HCT had good results [93]. Nutritional support should not be forgotten in these patients, and in patients with celiac disease a strict gluten-free diet is necessary [94].

Follow-Up

Recurrences are common in all lymphomas and intestinal lymphomas should be observed for possible recurrence. For instance, the clinical course of patients with IPSID is generally one of exacerbations and remissions, with death frequently resulting from either progressive malnutrition and wasting or the development of an aggressive lymphoma. So, close follow-up is essential in gastrointestinal lymphomas. Biopsy is mandatory for confirmation of relapse.

After the completion of therapy, surveillance is undertaken by physical examination, laboratory tests, and appropriate imaging studies. For small intestinal lymphomas that are FDG-avid, PET may be repeated in addition to or in lieu of CT. Although there have been no randomized controlled trials to compare what would be the best follow-up program for patients with gastrointestinal lymphomas, surveillance of patients should be akin to other lymphomas and gastrointestinal cancers. Patients need to be monitored for relapse and toxicity of treatments. During first 2 years, patients may be seen every 3–4 months. After 2 years of complete remission, visits can be scheduled for every 6 months until 5 years of disease onset. At the fifth year of disease, patients should be seen annually.

Primary Colorectal Lymphomas

The vast majority of colorectal lymphomas are secondary involvement of a systemic lymphoma. Primary colorectal lymphoma is an extremely rare entity that accounts for 0.2% of all colorectal malignancies [95]. Lymphomas of the large intestine are less common than those involving the small intestine. However, the cecum and rectum are affected more often than the remainder of the large intestine because of the relatively abundant lymphoid tissue in these sites. Only 3% of gastrointestinal lymphomas comprise colorectal lymphomas [7, 8]. Colorectal lymphoma differs from its gastric counterpart not only in pathology but also in its presentation, treatment, and prognosis.

Most of the colorectal lymphomas are non-Hodgkin lymphoma, and they are usually of B-cell origin. The most common histological subtype affecting the colorectal region is diffuse large B-cell lymphoma (DLBCL). It has a generally aggressive course and is composed of rapidly proliferating cells of B-cell lineage. The second most common colorectal lymphoma is MALT lymphoma that is a low-grade tumor arising from B cells associated with mucosal immunity. Colorectal MALT lymphomas do not have the same association with *H. pylori* infection as in the stomach and, therefore, they behave and are treated as a different clinical entity. Even though gastrointestinal involvement with systemic disease in mantle cell lymphoma (MCL) is seen more commonly, primary colorectal MCL is also described that has a male predominance and generally poor prognosis. T-cell lymphoma and Hodgkin's lymphoma affecting the colon have been reported but are exceedingly rare. T-cell lymphoma of the colorectal region is known to have a poorer prognosis and is rare in the Western world.

Colorectal lymphomas predominantly affect males in their sixth decade. Clinical presentation is akin to colorectal adenocarcinoma. Disease may present with abdominal pain, loss of weight, a palpable mass, overt or occult bleeding, diarrhea, or, rarely, bowel obstruction. In colorectal lymphomas, obstruction is less frequent than in other gastrointestinal lymphomas. Intussusception and perforation are other rare symptoms. T-cell lymphoma may present with colonic perforation [96]. Intussusception is usually associated with cecal involvement of lymphoma.

Possible risk factors such as inflammatory bowel disease, radiation, HIV, and other conditions relating to immunosuppression might be related to primary colorectal lymphoma. In a small study with 7 patients, 3 of them were found to be HIV positive [97]. Unlike its histological equivalents in the stomach and small intestine, MALT lymphomas of the colorectal region are not associated with infectious agents such as *H. pylori* or *C. jejeni*, respectively.

In colorectal lymphoma, presentation with a bulky disease of greater than 5 cm is seen in more than half of patients and sometimes may be palpated on physical examination. If there is any suspicion of colorectal lymphoma, colonoscopy with biopsy is the main diagnostic modality. Colorectal lymphoma can be hardly distinguished from adenocarcinoma of this region. Although there is not any specific colonoscopic appearance, multiple biopsies may reveal a lymphoma subtype [98]. Radiological clues such as larger lesion with longer segment involvement suggest lymphoma rather than adenocarcinoma. Histopathological evaluation of tissue is essential to reach a correct diagnosis.

Polypoid, infiltrative, colonic wall thickness, and mucosal nodularity are common radiological patterns. Double-contrast barium enema may show a lesion with extensive mucosal ulceration. Cavitary mass, focal strictures, or aneurismal dilatations may be seen. In MCL, typical small nodular and polypoid tumors also known as multiple lymphomatous polyposis may be seen endoscopically or with CT scan. Polyposis may also be associated with colorectal MALT lymphoma. Moreover, polyposis may be indistinguishable from familial adenomatous polyposis [74, 99].

There is no particular staging system for colorectal lymphomas. Correspondingly, colorectal lymphomas are staged like other gastrointestinal lymphomas. Baseline laboratory studies and CT scan of the thorax and abdomen with bone marrow biopsy and aspiration to determine the spread of disease should be performed. According to histological subtype, PET scan may be used for staging and for diagnosis of the gastrointestinal tract as the primary site. Lymphoma subtypes that are seen in the colon or rectum are typically FDG-avid.

Optimal treatment of colorectal lymphoma is not well established because of its rarity. There is no prospective randomized trial in colorectal lymphoma. Data from retrospective, small studies and case reports guide management of this rare entity. Some investigators suggest a combined modality approach; including surgery and chemotherapy. On the other hand, others reserve surgery for cases with intractable bleeding, perforation, or obstruction. Several authors believe that surgery provides important prognostic data and may offer a chance for cure. Adjuvant chemotherapy should also be considered in some types of colorectal lymphoma. Treatment should involve a multidisciplinary team and be dependent on the subtype of lymphoma. As with localized MALT lymphoma of other sites, colorectal MALT lymphoma may be treated with local therapies such as surgical excision and radiotherapy. A rare complication, chemotherapy-associated bowel perforation may be seen in the case of transmural involvement where urgent surgery is indicated [100]. Unresectable disease or chemoresistant tumors may be handled with radiotherapy.

Although chemotherapy remains the mainstay of management of aggressive lymphomas, the vast majority of patients undergo surgery. The regimens containing cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or addition of rituximab to CHOP are first-line therapies according to the cell of origin. Adjuvant chemotherapy should be considered in patients who were treated primarily by surgery. Although the mainstay of treatment of Burkett's lymphoma is chemotherapy, sometimes surgical resection may be required in the colorectal region. Management of colorectal DLBCL is similar to DLBCL of other parts of the gastrointestinal system. Results of the addition of rituximab to CHOP are satisfactory – similar to DLBCL of other sites. Involved field radiation therapy may also improve responses. Curative approach to MCL, which is primarily seen in elderly men, consists of chemotherapy followed by radiation of 30 Gy to the involved site [101]. Radiotherapy with lower doses may also play a role in a palliative setting, especially in bleeding in colorectal lymphomas.

Close follow-up is necessary to identify recurrent disease. Thus patients should be monitored with physical examination and imaging regularly like other lymphomas. Recurrences are common in colorectal lymphomas and patients generally die from their disease. Recurrence rates range from 33% to 75%, and recurrences can occur early or late. Most recurrences occur within the first 5 years after resection [102]. Generally, patients have recurrences with diffuse disease. These patients can be managed with salvage chemotherapy, but most ultimately die from disseminated lymphoma.

Extranodal Involvement of Gastrointestinal Tract by Systemic Lymphomas

Non-Hodgkin lymphomas represent the seventh most common type of cancer diagnosed annually in men in the developed countries and the sixth most common type in women

[60]. The incidence of NHL has increased significantly in past five decades due to the increasing exposure to carcinogens and the increasing prevalence of immunosuppressed individuals. The main clinical feature is nodal involvement, but 40% of NHL cases will present with a primary or secondary extranodal involvement and the extranodal disease has a worse prognosis [100]. Secondary involvement of extranodal tissue as part of generalized lymphoma is more common than primary extranodal disease in which there is a dominant extranodal component without or with minor nodal involvement. The GI tract is the most common extranodal site involved, with lymphoma accounting for 5–20% of all cases [103]. Systemic lymphomas may secondarily involve the GI tract. However, the subtypes of lymphomas that affect the GI tract primarily versus secondarily have not been comprehensively detailed.

Some criteria are used to distinguish between the primary and secondary extranodal GI NHL. The presence of peripheral lymphadenopathies at the time of presentation, enlarged mediastinal lymph nodes, abnormal white blood cell count, and lymphomatous involvement of liver and spleen are suggestive of secondary extranodal involvement of GI NHL [5]. Secondary extranodal involvement of nodal lymphomas are usually present in the advanced stage and have a high prognostic value. In the retrospective series, the stomach is the most common involved localization followed by the small intestine and colon in secondary GI lymphomas [104].

Patients with systemic lymphomas usually present with a rapidly enlarging symptomatic mass – typically nodal enlargement in the neck, abdomen, or mediastinum, but may present as a mass lesion anywhere in the body. The clinical manifestations of secondary GI lymphomas depend principally on the involved site and can be lymphoma-related "B-symptoms." Site-related symptoms are mainly dyspepsia, abdominal pain, nausea or vomiting, and anorexia. Symptoms such as weight loss, vomiting, hematemesis/melena, and perforation are alarming and are more frequent in aggressive lymphomas [100, 105]. Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and Burkett's lymphoma (BL) are the dominant systemic histological subtypes in extranodal lymphomas, especially in the gastrointestinal tract. In this section, we would like to discuss the secondary GI involvement of systemic lymphomas with a review of the literature.

Epidemiology

DLBCL is the most common histological subtype of NHL and constitutes 30–35% of patients with NHL. It has an aggressive course in which survival without treatment is measured in months. In the United States, the incidence of DLBCL is approximately 7/100,000/year [106] and the crude incidence in Europe is 3.8/100000/year [107]. The incidence varies by ethnicity and increases with age; the median age at presentation is 64 years for patients as a whole, but appears to be younger for Blacks than for White Americans. In up to 40% of patients with DLBCL, the disease initially presents in an extranodal site, most commonly GI but also in the other sites. Secondary GI involvement is thought to be more common than primary involvement in DLBCL, however, retrospective studies show that primary involvement is more common [104, 108]. In retrospective studies, DLBCL is the most common type of systemic lymphoma secondarily involving the GI tract. Warrick et al. [108] retrospectively evaluated the clinical, molecular, and histological features of North American primary and secondary GI lymphomas diagnosed from 2000 to 2009 seen at their institution. DLBCL was the most common lymphoma type to secondarily involve the GI tract, accounting for the majority of intestinal (57%), gastric (80%), and esophageal (100%) cases.

Follicular lymphoma is a prototype of indolent lymphoma accounting for 20% of new lymphomas and is the second most common NHL subtype worldwide. The annual incidence of this disease has rapidly increased during recent decades and has risen from 2–3/100,000 during the 1950s to 5–7/100,000 recently. Follicular lymphoma predominantly affects older adults. The incidence is slightly higher in females [109]. Most of the patients have widespread disease at the time of diagnosis, usually involving the lymph nodes. The involvement of spleen and bone marrow is not uncommon. Peripheral blood and extranodal sites involvement can occur occasionally. GI tract involvement usually occurs in the presence of widespread nodal disease [110].

MCL is one of the mature small B-cell NHLs that has a more aggressive behavior than indolent lymphomas. MCL represents approximately 6% of all lymphomas in the US and 7–9% in Europe. Its incidence is 0.51–0.55 per 100,000 persons in the US. Patients with MCL have a median age in their 60s and a striking male predominance (2:1) [111]. Patients generally have advanced disease and present with extensive lymphadenopathy, bone marrow involvement, splenomegaly, and gastrointestinal involvement. MCL can involve any region of the GI tract. While primary GI-MCL is even rarer, 77–88% of cases of advanced-stage nodal MCL have microscopic GI tract involvement [112, 113]. GI-MCL was previously considered synonymous with "multiple lymphomatous polyposis " (MLP), as it often presents with malignant polyps lining segments of the GI tract. A prospective clinicopathologic study of 31 cases of GI involvement found the following sites to be involved: stomach (57%), duodenum (52%), jejunum/ileum (87%), colon (90%), and rectum (69%). Lymphomatous submucosal nodules producing polypoid lesions were found in both the small bowel and colon in 28 of 31 cases [114].

Burkett's lymphoma is a highly aggressive B-cell lymphoma often presenting with bulky disease and a high tumor burden [115]. BL is responsible for 1–2% of lymphomas in adults and up to 40% in children in the USA and Western Europe [106]. Three variants of BL have been described: endemic (African), sporadic (non-endemic), and immunodeficiency-associated. Extranodal involvement is common in patients with all 3 variants. While involvement of the jaws and facial bones is present in about 50% of patients with endemic BL, jaw tumors are very rare in sporadic BL. The most common extranodal sites in patients with sporadic type BL are in the abdomen, especially the ileocecal region. Burkitt's lymphoma is also seen in the setting of HIV infection when it often involves the gastrointestinal tract, most commonly secondarily [64].

Etiology and Risk Factors

DLBCLs are characterized as a heterogeneous group of malignancies constituted of large cells with nuclei at least twice the size of a small lymphocyte and usually larger than those of tissue macrophages. They more often occur de novo but can also represent the progression or transformation of indolent B-cell lymphomas, such as chronic lymphocytic leukemia, marginal zone lymphoma, and follicular lymphoma [116]. DLBCL is frequently encountered in patients with both acquired and congenital immunologic deficiency diseases [117]. Patients chronically immunosuppressed by drugs, particularly after organ transplants, have a higher incidence of diffuse aggressive lymphomas, often in the gastrointestinal tract. The associations between DLBCL and viruses have become a matter of debate during the last decade. HIV infection [118], EBV infection [119], and HCV seropositivity [120] have been identified as risk factors of DLBCL. Patients with HIV infection have a higher risk of developing secondary gastrointestinal lymphomas due to hyperactivation of B cells. HIV-related lymphomas are generally high-grade B-cell lymphomas with poor prognosis and usually occur in multiple sites of the gastrointestinal tract. Many patients with DLBCL have secondary involvement of some part of the GI tract at the time of initial presentation, however, it is unclear how neoplastic lymphoid cells involve the GI tract. Wu et al. [121] showed that CCR9 expression in nodal B-cell lymphomas may be a strong indicator for concurrent or future GI involvement, especially in DLBCL and FL.

The development and progression of FL is a complex process and involves the interactions of multiple clinical risk factors such as environmental exposures, genetic, genomic, and epigenetic events like in other indolent lymphomas. There is increasing evidence that molecular risk factors may have independent participation to the risk of FL beyond clinical risk factors and environmental exposures. The most common acquired nonrandom chromosomal translocation in FL patients is the t(14; 18) translocation, which is found in more than 80% of all cases. This translocation, generated through the BCL-2/IGH rearrangement, results in the overexpression of the BCL-2 gene, which encodes apoptosis regulator proteins [122].

The etiology of MCL is still unknown for most patients. Several lifestyle factors and environmental risk factors have been suspected but not conclusively shown to be associated with MCL. Multiple viruses have been implicated in the development of NHL overall. However, according to an InterLymph study [123], there is still a lack of solid evidence for the association between these viral agents and the risk of MCL. Constant involvement of the gastrointestinal tract has been observed in MCL patients, leading to speculation that the risk of MCL development is associated with infectious agents that affect the gastrointestinal tract or cause a variation in microbial gut flora. The genetic feature of MCL is the t(11;14)(q13;q32) translocation, which leads to the overexpression of CCND1. The gene CCND1 can dysregulate cell cycle control by overcoming the suppressor effect of retinoblastoma 1(RB1) and the cell cycle inhibitor p27. Although the t(11;14)(q13;q32) translocation occurs in the majority of MCL cases, there have been reports of a small subset of tumors that do not overexpress CCND1 and these CCND1-negative patients had poor clinical outcomes [124].

BL has been reported as a common neoplasm in HIV-infected patients, and HIV-associated BL displays an activation of c-MYC by chromosome translocations that show structural similarities to those found in patients with sporadic BL. Nonetheless, most AIDS-related BLs in Western countries are EBV negative, whereas in Africa they are strongly associated with EBV. Chromosomal rearrangement of the proto-oncogene c-MYC is the genetic hallmark of BL: More than 80% of BL cases have a translocation of MYC at band q24 from chromosome 8 to the Ig heavy chain regions on chromosome 14, t(8;14) [125].

Diagnosis

The diagnosis of systemic lymphomas is best made by examining the excisional tissue biopsy, most commonly a lymph node. This allows assessment of nodal architecture and provides adequate material for phenotypic and molecular studies. While an excisional lymph node biopsy is the preferred diagnostic test for most patients, some patients do not present with overt lymphadenopathy and require the pathological evaluation of another tissue for diagnosis. The most important issue in this process is that the diagnosis of lymphomas should be carried out in a reference hematopathology laboratory with expertise in morphological interpretation.

The pathological diagnosis of DLBCL is based on morphology and immunophenotyping, which is essential to make the diagnosis. The tumor cells are of large size (e.g., nuclei at least twice the size of a small lymphocyte and larger than the nucleus of a tissue macrophage) and often resemble normal centroblasts or immunoblasts. In addition to the common centroblastic and immunoblastic morphologies, several other cytological variants are recognized (e.g., multilobated and anaplastic), but their clinical significance is debated. The characteristic immunophenotype of DLBCL consists of expression of CD19 and CD20 without expression of CD5 or CD23. BCL2 and BCL6 are expressed at different ranges in many cases [126]. Some studies show that DNA microarray analysis suggests there are at least three distinct subgroups within DLBCL called germinal centers like B cell, an activated B-cell type, and primary mediastinal B-cell DLBCL. The activated B-cell type has a worse prognosis even within subgroups of the International Prognostic Index (IPI) [127].

FL is a malignancy of germinal center B cells, usually with a predominantly follicular pattern. Composed of a mixture of centrocytes and centroblasts, at least a partially follicular pattern is typical for the histological diagnosis. The proportion of centroblasts varies from case to case and the clinical course occurs more aggressively with increasing rates of centroblasts. The WHO classification is based on the centroblast counting method of Mann and Berard that assigns cases into grade 1 to 3B [128]. Grade 1 or 2 GI-FL accounts for the majority of cases. Typically, the neoplastic cells express B-cell markers CD19, CD20, and CD22 and are BCL2 +, BCL6 +, CD10 +, CD5 −, and CD43 −. The presence of t (14; 18) (q32; q21) is the characteristic cytogenetic clinical feature of FL, present in up to 90% of cases [129].

In MCL, there is a proliferation of small- to medium-sized monomorphic malignant B cells, with irregular nuclei and restricted cytoplasm. In the early stages there may be a mantle zone or nodular pattern. Four cytological variants of MCL are defined, including the small cell variant, mantle zone variant, diffuse variant, and the plastic variant [130]. Immunophenotyping is commonly used with the MCL cells being CD20, CD5, and positive for Cyclin D1 while being negative for CD10 and Bcl6. The hallmark chromosomal translocation t (11:14) (q13; 32) identifies MCL, and can be shown in most cases [124]. This translocation leads to the aberrant expression of cyclin D1, which is not typically expressed in normal lymphocytes. Overexpression of the transcription factor SOX11 is a newer diagnostic marker, identified in both cyclin D1-positive and cyclin D1-negative MCL, which distinguishes cyclin D1-negative MCL from other indolent NHLs [131].

BL is characterized by an exceptionally high proliferation rate (100% Ki 67 positivity), a mature B-cell immunophenotype (CD10, CD19, CD20, CD22, CD43, and BCL6 positivity), and a high histologic appearance demonstrating diffuse infiltration with a starry-sky pattern of macrophages phagocytosing apoptotic tumor cells. Chromosomal rearrangement of the proto-oncogene c-MYC is the genetic feature of BL: Most BL cases have a translocation of MYC at band q24 from chromosome 8 to the Ig heavy chain regions on chromosome 14, t(8;14). Less frequently, rearrangements translocate c-MYC to a position close to the antibody genes in chromosome 2 or 22 [125].

Staging

Appropriate staging is important in the clinical management of patients with lymphomas for treatment strategy, response assessment, and surveillance. Staging of the secondary GI lymphomas should be performed as systemic nodal lymphomas. The standard staging system used for systemic lymphomas was proposed at the Ann Arbor Conference in 1971 [132]. This staging system shows the number of sites of involvement and their relation to the diaphragm, the presence of B symptoms, and the presence of extranodal disease. A careful history and physical examination are the most important factors in the patient's true evaluation in systemic lymphomas. The physical includes the examination of all lymph node enlargements, recording the sites and sizes of all abnormal lymph nodes, inspection of Waldeyer's ring, evaluation of the presence or absence of hepatosplenomegaly, inspection of the skin, and detection of palpable masses. The presence or absence of B symptoms should be noted, and other symptoms may show specific sites of involvement. An assessment of performance status according to the Eastern Cooperative Oncology Group (ECOG) scale is important in all patients, and especially for those entering into clinical research trials.

Laboratory studies that should be routinely performed in NHL patients include a complete blood count to assess bone marrow reserves and a white blood cell differential with careful examination of the peripheral blood to look for the presence of circulating lymphoma cells. Serum chemistry should include an assessment of hepatic and renal function. Lactic dehydrogenase (LDH) is also an important indicator of tumor activity and is included in the International Prognostic Index. The uric acid level may predict patients at increased risk for urate nephropathy. A test for a complete assessment of HIV, HBV, and HCV should be performed in all patients [133].

A bone marrow aspirate and biopsy should be performed in all patients. Additional testing in systemic lymphomas may include lumbar puncture to assess liquor cytology identifying subclinical meningeal involvement and brain MRI in patients with high risk of central nervous system (CNS) progression. Fluorodeoxyglucose positron emission

tomography (FDG-PET) is now a standard procedure both for staging and response assessment. Many studies showed that PET at the end of treatment is highly predictive of progression-free survival (PFS) and overall survival (OS) in aggressive lymphomas with or without residual masses detected with CT scan [134]. Endoscopy and colonoscopy is usually performed only in patients who have GI symptoms, such as diarrhea, abdominal pain, nausea, and vomiting or in patients who have suspicious imaging findings on CT/PET CT. Nevertheless, some trials suggest that practically most of the patients with aggressive MCL will have GI tract involvement at the time of diagnosis. A relevant issue is whether this area needs to be evaluated at the end of therapy to document true complete disease remission in MCL patients [112].

Treatment

Secondary GI lymphomas are generally in advanced stage at the time of presentation and have high prognostic index. Rituximab-based chemotherapy is the cornerstone of the treatment in secondary GI lymphomas. Sometimes presentation of lymphoma requires initial management by surgery. If there is a complication such as obstruction, bleeding, or perforation at initial presentation, immediate surgical intervention should be required. R-CHOP that is used in the nodal form of lymphoma may also improve outcome in gastrointestinal DLBCL. Treatment strategies should be stratified according to age, IPI, and feasibility of dose-intensified approaches. In cases with high tumor burden, bulky disease, precautions such as the administration of steroids several days as "prephase" treatment are recommended to avoid tumor lysis syndrome. Neutropenic fever requires prophylactic use of hematopoietic growth factors in patients treated with curative intent and in patients older than 60 years of age [126]. The nodal DLBCL with non-bulky limited stage are treated with combined modality therapy consisting of abbreviated systemic chemotherapy (i.e., three cycles of R-CHOP) and involved field radiation therapy. An acceptable alternative is the administration of full course (6–8 cycles) systemic chemotherapy plus rituximab without radiation [135]. Secondary GI DLBCL has high IPI score and aggressive clinical course, and therefore it is recommended to administer 6–8 cycles of R-CHOP chemotherapy similar to the treatment of the high-risk nodal lymphomas [126]. The activated B-cell (ABC) subtype has been shown to have a worse prognosis when compared with germinal center B-cell (GCB) in patients treated by R-CHOP. The ABC subtype is characterized by a constitutive activation of the NF-κ(kappa)B pathway, which could be targeted by different agents as bortezomib, lenalidomide, and ibrutinib [136, 137]. Induction and consolidation regimens should be used and autologous hematopoietic cell transplantation (HCT) should be recommended in appropriate patients [126].

For prognostic purposes, a "Follicular Lymphoma-specific International Prognostic Index" (FLIPI) has been established for FL. A revised FLIPI-2 (incorporating β[beta]2-microglobulin, diameter of largest lymph node, bone marrow involvement, and hemoglobin level) has been recently suggested for patients requiring treatment. Individualized management is essential in FL. Treatment should be reserved for the symptomatic phase of the disease, disrupted normal marrow function, or rapidly progressive disease. In the case of higher histological grade, advanced stage, and/or poor prognosis factors, the management includes rituximab with combination chemotherapy. Multiple regimens used in other B-cell lymphomas have demonstrated activity in FL, including CHOP and CVP (cyclophosphamide, vincristine, and prednisone) as well as fludarabine-based regimens (fludarabine and cyclophosphamide [FC]; fludarabine, cyclophosphamide, and mitoxantrone [FCM]), chlorambucil, and bendamustine in combination with rituximab. Maintenance rituximab therapy for 2 years is the standard of care for all patients who achieve a response from systemic treatment, as evidence suggests improved outcomes in both the first- and second-line setting [138]. Autologous stem cell transplant or allogeneic transplant are the other treatment options in selected patients in case of more aggressive disease.

MCL is usually responsive to a variety of initial therapies, but relatively short-term remissions are obtained with conventional chemotherapy regimens. The median duration of remission in most trials is 1.5–3 years and the median OS is 3–6 years with standard chemotherapy. The Mantle cell International Prognostic Index (MIPI) was produced by the European MCL Network [139]. The independent prognostic factors for shorter OS from the MIPI were higher age, worse ECOG performance status, higher LDH, and a higher white blood cell count at diagnosis. These were calculated as a continuous parameter and three groups emerged: (1) MIPI low-risk with the median OS not reached (5-yr OS 60%), (2) MIPI intermediate-risk with a median OS of 51 months, and (3) a MIPI high-risk group with a median OS of 29 months. Asymptomatic elderly or low-MIPI patients can be observed without any therapy. When the patients become symptomatic, first-line therapy choices include R-CHOP, R-Bendamustine, or a clinical trial [130, 140]. For young symptomatic patients with MCL, considerations include R-HyperCVAD with high-dose cytarabine and methotrexate followed by ASCT in first complete remission for appropriate patients. For patients who are not candidates for standard R-HyperCVAD with high-dose cytarabine/methotrexate, possible alternatives include R-CHOP, R-CHOP alternating with R-DHAP, or R-Bendamustine [130, 141]. In relapsed/refractory MCL, different novel treatment options based on targeting known

signaling pathways have been tested. Ibrutinib is a brutons thyrosine kinase inhibitor and should be considered for relapsed MCL patients [142]. Bendamustine/rituximab is an option in patients who have not previously received bendamustine. Other options would include a bortezomib-containing regimen or lenalidomide or a clinical trial. If the patient is a candidate for stem cell transplantation, autologous transplant remission or a reduced intensity allogeneic stem cell transplant should be considered [130].

Chemotherapy for BL has traditionally involved intensive therapy with regimens such as R-HyperCVAD, CODOX-M/IVAC, using treatment principles reminiscent of those employed for acute lymphoblastic leukemia including routine CNS prophylaxis. Biochemical abnormalities should be corrected rapidly before treatment and patients should receive prophylactic rasburicase and hydration [143].

Follow-Up

Patients with systemic lymphomas who are event-free at 3 years have a significantly reduced risk of recurrence, emphasizing the need for monitoring the disease in this early period. It is recommended that careful history and physical examination should occur every 3–4 months for 3 years, every 6 months for 2 more years, and then once a year with attention to development of secondary tumors or other long-term side effects of chemotherapy [126, 129, 130]. Blood count should be carried out at 3, 6, 12, and 24 months and then only as needed for evaluation of suspicious symptoms or clinical findings in those patients suitable for further therapy. There is no evidence that routine imaging in patients in complete remission provides any outcome advantage, and it may increase the incidence of secondary malignancies. Routine surveillance with PET scan is not recommended. High-risk patients with curative options may potentially mandate more frequent evaluation.

References

1. Paryani S, Hoppe RT, Burke JS, Sneed P, Dawley D, Cox RS, et al. Extralymphatic involvement in diffuse non-Hodgkin's lymphoma. J Clin Oncol. 1983;1(11):682–8.
2. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer. 1972;29:252–60.
3. Loehr WJ, Mujahed Z, Zahn FD, Gray GF, Thorbjarnarson B. Primary lymphoma of the gastrointestinal tract: a review of 100 cases. Ann Surg. 1969;170(2):232–8.
4. Gurney KA, Cartwright RA. Increasing incidence and descriptive epidemiology of extranodal non-Hodgkin lymphoma in parts of England and Wales. Hematol J. 2002;3(2):95–104.
5. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumors of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg. 1961;49:80.
6. Lewin KJ, Ranchod M, Dorfman RF. Lymphomas of the gastrointestinal tract: a study of 117 cases presenting with gastrointestinal disease. Cancer. 1978;42:693.
7. Koch P, del Valle F, Berdel WE, Willich NA, Reers B, Hiddemann W, et al; German Multicenter Study Group. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92. J Clin Oncol. 2001;19(18):3861–73.
8. Papaxoinis G, Papageorgiou S, Rontogianni D, Kaloutsi V, Fountzilas G, Pavlidis N, et al. Primary gastrointestinal non-Hodgkin's lymphoma: a clinicopathologic study of 128 cases in Greece. A Hellenic Cooperative Oncology Group study (HeCOG). Leuk Lymphoma. 2006;47(10):2140–6.
9. Cogliatti SB, Schmid U, Schumacher U, Eckert F, Hansmann ML, Hedderich J, et al. Primary B-cell gastric lymphoma: a clinicopathological study of 145 patients. Gastroenterology. 1991;101:1159–70.
10. Müller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Ann Hematol. 2005;84:1–12.
11. Brands F, Monig SP, Raab M. Treatment and prognosis of gastric lymphoma. Eur J Surg. 1997;163:803–13.
12. Zucca E, Bertoni F, Roggero E, Bosshard G, Cazzaniga G, Pedrinis E, et al. Molecular analysis of the progression from Helicobacter pylori-associated chronic gastritis to mucosa-associated lymphoid-tissue lymphoma of the stomach. N Engl J Med. 1998;338:804–10.
13. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. Lancet. 1991;338:1175.
14. Aull MJ, Buell JF, Peddi VR, Trofe J, Beebe TM, Hanaway MJ, et al; Israel Penn International Transplant Tumor Registry. MALToma: a Helicobacter pylori-associated malignancy in transplant patients: a report from the Israel Penn International Transplant Tumor Registry with a review of published literature. Transplantation. 2003;75(2):225–8.
15. McTamaney JP, Neifeld JP, Mendez-Picon G, Lee HM. Primary gastric lymphoma following renal transplantation. J Surg Oncol. 1981;18:265.
16. Heise W, Arastéh K, Mostertz P, Skörde J, Schmidt W, Obst C, et al. Malignant gastrointestinal lymphomas in patients with AIDS. Digestion. 1997;58:218.
17. Whooley BP, Bernik S, Sarkis AY, Wallack MK. Primary gastrointestinal non-Hodgkin's lymphoma: increasingly AIDS-related. Am Surg. 1998;64:137.
18. Andrews CN, John Gill M, Urbanski SJ, Stewart D, Perini R, Beck P. Changing epidemiology and risk factors for gastrointestinal non-Hodgkin's lymphoma in a North American population: population-based study. Am J Gastroenterol. 2008;103:1762.
19. Catassi C, Fabiani E, Corrao G, Barbato M, De Renzo A, Carella AM, et al. Risk of non-Hodgkin lymphoma in celiac disease. JAMA. 2002;287:1413.
20. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005;54:1121.
21. Geborek P, Bladström A, Turesson C, Gulfe A, Petersson IF, Saxne T, et al. Tumor necrosis factor blockers do not increase overall tumor risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005;64(5):699–703.
22. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54(3):692–701.

23. Mathus-Vliegen EMH, Van Halteren H, Tytgat GNJ. Malignant lymphoma in coeliac disease: various manifestations with distinct symptomatology and prognosis? J Intern Med. 1994;236:43–9.
24. Radaszkiewicz T, Dragosics B, Bauer P. Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. Gastroenterology. 1992;102:1628.
25. Wang T, Gui W, Shen Q. Primary gastrointestinal non-Hodgkin's lymphoma: clinicopathological and prognostic analysis. Med Oncol. 2010;27:661.
26. Caletti G, Ferrari A, Brocchi E, Barbara L. Accuracy of endoscopic ultrasonography in the diagnosis and staging of gastric cancer and lymphoma. Surgery. 1993;113:14.
27. Fujishima H, Misawa T, Maruoka A, Chijiiwa Y, Sakai K, Nawata H. Staging and follow-up of primary gastric lymphoma by endoscopic ultrasonography. Am J Gastroenterol. 1991;86:719.
28. Vilmann P, Hancke S, Henriksen FW, Jacobsen GK. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of lesions in the upper gastrointestinal tract. Gastrointest Endosc. 1995;41:230.
29. Spinelli P, Lo Gullo C, Pizzetti P. Endoscopic diagnosis of gastric lymphomas. Endoscopy. 1980;12:211.
30. Fork FT, Haglund U, Högström H, Wehlin L. Primary gastric lymphoma versus gastric cancer. An endoscopic and radiographic study of differential diagnostic possibilities. Endoscopy. 1985;17:5.
31. Suekane H, Iida M, Yao T, Matsumoto T, Masuda Y, Fujishima M. Endoscopic ultrasonography in primary gastric lymphoma: correlation with endoscopic and histologic findings. Gastrointest Endosc. 1993;39:139–45.
32. Novak U, Basso K, Pasqualucci L, Dalla-Favera R, Bhagat G. Genomic analysis of non-splenic marginal zone lymphomas (MZL) indicates similarities between nodal and extranodal MZL and supports their derivation from memory B-cells. Br J Haematol. 2011;155:362.
33. Nakamura S, Matsumoto T, Nakamura S, Jo Y, Fujisawa K, Suekane H, Yao T, Tsuneyoshi M, Iida M. Chromosomal translocation t(11;18)(q21;q21) in gastrointestinal mucosa associated lymphoid tissue lymphoma. J Clin Pathol. 2003;56:36–42.
34. Bertoni F, Zucca E. Delving deeper into MALT lymphoma biology. J Clin Invest. 2006;116:22.
35. Dierlamm J, Baens M, Wlodarska I, Stefanova-Ouzounova M, Hernandez JM, Hossfeld DK, et al. The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11;18) (q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. Blood. 1999;93:3601–9.
36. Yeh KH, Kuo SH, Chen LT, Mao TL, Doong SL, Wu MS, et al. Nuclear expression of BCL10 or nuclear factor kappa B helps predict Helicobacter pylori-independent status of low-grade gastric mucosa-associated lymphoid tissue lymphomas with or without t(11;18)(q21;q21). Blood. 2005;106:1037–41.
37. Park YH, Kim WS, Bang SM, Lee SI, Uhm JE, Kang HJ, et al. Prognostic factor analysis and proposed prognostic model for conventional treatment of high-grade primary gastric lymphoma. Eur J Haematol. 2006;77:304–8.
38. Klapproth K, Wirth T. Advances in the understanding of MYC-induced lymphomagenesis. Br J Haematol. 2010;149:484–97.
39. Iqbal J, Neppalli VT, Wright G, Dave BJ, Horsman DE, Rosenwald A, et al. BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. J Clin Oncol. 2006;24:961–8.
40. Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30:3452–9.
41. Perry C, Herishanu Y, Metzer U, Bairey O, Ruchlemer R, Trejo L, et al. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. Eur J Haematol. 2007;79:205.
42. Zucca E, Copie-Bergman C, Ricardi U, Thieblemont C, Raderer M, Ladetto M, Ladetto M, ESMO Guidelines Working Group. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi144–8.
43. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059–68.
44. Musshoff K, Schmidt-Vollmer H. Proceedings: prognosis of non-Hodgkin's lymphomas with special emphasis on the staging classification. Z Krebsforsch Klin Onkol Cancer Res Clin Oncol. 1975;83(4):323–41.
45. Rohatiner A, d'Amore F, Coiffier B, Crowther D, Gospodarowicz M, Isaacson P, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol. 1994;5(5):397–400.
46. Ruskoné-Fourmestraux A, Dragosics B, Morgner A, Wotherspoon A, De Jong D. Paris staging system for primary gastrointestinal lymphomas. Gut. 2003;52(6):912–3.
47. Inagaki H, Nakamura T, Li C, Sugiyama T, Asaka M, Kodaira J, et al. Gastric MALT lymphomas are divided into three groups based on responsiveness to Helicobacter Pylori eradication and detection of API2-MALT1 fusion. Am J Surg Pathol. 2004;28:1560–7.
48. Xia B, Zhang L, Guo SQ, Li XW, Qu FL, Zhao HF, et al. Coexpression of MYC and BCL-2 predicts prognosis in primary gastrointestinal diffuse large B-cell lymphoma. World J Gastroenterol. 2015;21:2433–42.
49. Nakamura S, Sugiyama T, Matsumoto T, Iijima K, Ono S, Tajika M, et al. Long-term clinical outcome of gastric MALT lymphoma after eradication of Helicobacter pylori: a multicentre cohort follow-up study of 420 patients in Japan. Gut. 2012;61:507–13.
50. Alpen B, Neubauer A, Dierlamm J, Marynen P, Thiede C, Bayerdörfer E, et al. Translocation t(11;18) absent in early gastric marginal zone B-cell lymphoma of MALT type responding to eradication of Helicobacter pylori infection. Blood. 2000;95:4014–5.
51. Neubauer A, Thiede C, Morgner A, Alpen B, Ritter M, Neubauer B, et al. Cure of Helicobacter pylori infection and duration of remission of low-grade gastric mucosa-associated lymphoid tissue lymphoma. J Natl Cancer Inst. 1997;89:1350–5.
52. Conconi A, Martinelli G, Thiéblemont C, Ferreri AJ, Devizzi L, Peccatori F, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood. 2003;102:2741–5.
53. Martinelli G, Laszlo D, Ferreri AJ, Pruneri G, Ponzoni M, Conconi A, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. J Clin Oncol. 2005;23:1979–83.
54. Raderer M, Streubel B, Wöhrer S, Häfner M, Chott A. Successful antibiotic treatment of Helicobacter pylori negative gastric mucosa associated lymphoid tissue lymphomas. Gut. 2006;55:616–8.
55. Daum S, Ullrich R, Heise W, Dederke B, Foss HD, Stein H, et al. Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on Intestinal non-Hodgkin's Lymphoma. J Clin Oncol. 2003;21:2740–6.
56. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet. 1993;342:575–7.
57. Shiozawa E, Norose T, Kaneko K, Yamochi-Onizuka T, Takimoto M, Imawari M, et al. Clinicopathological comparison of the World Health Organization/Wotherspoon score to the Grouped'Etude

des Lymphomes de l'Adult grade for the post-treatment evaluation of gastric mucosa-associated lymphoid tissue lymphoma. J Gastroenterol Hepatol. 2009;24:307–15.
58. Ruskoné-Fourmestraux A, Fischbach W, Aleman BM, Boot H, Du MQ, Megraud F, EGILS group. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. Gut. 2011;60:747–58.
59. Zucca E, Dreyling M, ESMO Guideline Working Group. Gastric marginal zone lymphoma of MALT type: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21:175–6.
60. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
61. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. Ann Epidemiol. 2009;19(1):58–69.
62. Isaacson PG. Gastrointestinal lymphoma. Hum Pathol. 1994;25(10):1020–9.
63. Al-Saleem T, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. Blood. 2005;105(6):2274–80.
64. Bibas M, Antinori A. EBV and HIV-Related Lymphoma. Mediterr J Hematol Infect Dis. 2009;1(2):e2009032.
65. Delabie J, Holte H, Vose JM, Ullrich F, Jaffe ES, Savage KJ, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. Blood. 2011;118(1):148–55.
66. Quintanilla-Martinez L, Lome-Maldonado C, Ott G, Gschwendtner A, Gredler E, Angeles-Angeles A, et al. Primary intestinal non-Hodgkin's lymphoma and Epstein-Barr virus: high frequency of EBV-infection in T-cell lymphomas of Mexican origin. Leuk Lymphoma. 1998;30(1–2):111–21.
67. Lecuit M, Abachin E, Martin A, Poyart C, Pochart P, Suarez F, Bengoufa D, et al. Immunoproliferative small intestinal disease associated with Campylobacter jejuni. N Engl J Med. 2004;350(3):239–48.
68. Nikbin B, Banisadre M, Ala F, Mojtabai A. HLA AW19, B12 in immunoproliferative small intestinal disease. Gut. 1979;20(3):226–8.
69. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. 2001;91(4):854–62.
70. Cooper BT, Holmes GK, Ferguson R, Cooke WT. Celiac disease and malignancy. Medicine (Baltimore). 1980;59(4):249–61.
71. Asano N, Kato S, Nakamura S. Epstein-Barr virus-associated natural killer/T-cell lymphomas. Best Pract Res Clin Haematol. 2013;26(1):15–21.
72. Heise W. GI-lymphomas in immunosuppressed patients (organ transplantation; HIV). Best Pract Res Clin Gastroenterol. 2010;24(1):57–69.
73. Castellano G, Moreno D, Galvao O, Ballestín C, Colina F, Mollejo M, et al. Malignant lymphoma of jejunum with common variable hypogammaglobulinemia and diffuse nodular hyperplasia of the small intestine. A case study and literature review. J Clin Gastroenterol. 1992;15(2):128–35.
74. Ghai S, Pattison J, Ghai S, O'Malley ME, Khalili K, Stephens M. Primary gastrointestinal lymphoma: spectrum of imaging findings with pathologic correlation. Radiographics. 2007;27(5):1371–88.
75. Juweid M, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25(5):571–8.
76. Cronin CG, Scott J, Kambadakone A, Catalano OA, Sahani D, Blake MA, et al. Utility of positron emission tomography/CT in the evaluation of small bowel pathology. Br J Radiol. 2012;85(1017):1211–21.
77. Chung HH, Kim YH, Kim JH, Cha SH, Kim BH, Kim TK, et al. Imaging findings of mantle cell lymphoma involving gastrointestinal tract. Yonsei Med J. 2003;44(1):49–57.
78. Schmatz AI, Streubel B, Kretschmer-Chott E, Püspök A, Jäger U, Mannhalter C, et al. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. J Clin Oncol. 2011;29(11):1445–51.
79. Joyce AM, Burns DL, Marcello PW, Tronic B, Scholz FJ. Capsule endoscopy findings in celiac disease associated enteropathy-type intestinal T-cell lymphoma. Endoscopy. 2005;37(6):594–6.
80. Yamamoto S, Nakase H, Yamashita K, Matsuura M, Takada M, Kawanami C, et al. Gastrointestinal follicular lymphoma: review of the literature. J Gastroenterol. 2010;45(4):370–88.
81. Al-Saleem TI, Qadiry WA, Issa FS, King J. The immunoselection technic in laboratory diagnosis of alpha heavy-chain disease. Am J Clin Pathol. 1979;72(1):132–3.
82. Suzuki R. NK/T-cell lymphomas: pathobiology, prognosis and treatment paradigm. Curr Oncol Rep. 2012;14(5):395–402.
83. Kim SJ, Kang HJ, Kim JS, Oh SY, Choi CW, Lee SI, et al. Comparison of treatment strategies for patients with intestinal diffuse large B-cell lymphoma: surgical resection followed by chemotherapy versus chemotherapy alone. Blood. 2011;117(6):1958–65.
84. Aleman BM, Haas RL, van der Maazen RW. Role of radiotherapy in the treatment of lymphomas of the gastrointestinal tract. Best Pract Res Clin Gastroenterol. 2010;24(1):27–34.
85. Azab MB, Henry-Amar M, Rougier P, Bognel C, Theodore C, Carde P, et al. Prognostic factors in primary gastrointestinal non-Hodgkin's lymphoma. A multivariate analysis, report of 106 cases, and review of the literature. Cancer. 1989;64(6):1208–17.
86. Ben-Ayed F, Halphen M, Najjar T, Boussene H, Jaafoura H, Bouguerra A, et al. Treatment of alpha chain disease. Results of a prospective study in 21 Tunisian patients by the Tunisian-French intestinal Lymphoma Study Group. Cancer. 1989;63(7):1251–6.
87. el Saghir NS. Combination chemotherapy with tetracycline and aggressive supportive care for immunoproliferative small-intestinal disease lymphoma. J Clin Oncol. 1995;13(3):794–5.
88. Shih L, Liaw SJ, Dunn P, Kuo TT. Primary small-intestinal lymphomas in Taiwan: immunoproliferative small-intestinal disease and nonimmunoproliferative small-intestinal disease. J Clin Oncol. 1994;12(7):1375–82.
89. Lee J, Kim WS, Kim K, Ahn JS, Jung CW, Lim HY, et al. Prospective clinical study of surgical resection followed by CHOP in localized intestinal diffuse large B cell lymphoma. Leuk Res. 2007;31(3):359–64.
90. Foon KA, Takeshita K, Zinzani PL. Novel therapies for aggressive B-cell lymphoma. Adv Hematol. 2012;2012:302570.
91. Yamaguchi M, Suzuki R, Kwong YL, Kim WS, Hasegawa Y, Izutsu K, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci. 2008;99(5):1016–20.
92. Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418–25.
93. Sieniawski M, Angamuthu N, Boyd K, Chasty R, Davies J, Forsyth P, et al. Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. Blood. 2010;115(18):3664–70.

94. Nijeboer P, Malamut G, Mulder CJ, Cerf-Bensussan N, Sibon D, Bouma G, et al. Enteropathy-associated T-cell lymphoma: improving treatment strategies. Dig Dis. 2015;33(2):231–5.
95. Dionigi G, Annoni M, Rovera F, Boni L, Villa F, Castano P, et al. Primary colorectal lymphomas: review of the literature. Surg Oncol. 2007;16(Suppl 1):S169–71.
96. Kim YH, Lee JH, Yang SK, Kim TI, Kim JS, Kim HJ, et al. Primary colon lymphoma in Korea: a KASID (Korean Association for the Study of Intestinal Diseases) Study. Dig Dis Sci. 2005;50(12):2243–7.
97. Doolabh N, Anthony T, Simmang C, Bieligk S, Lee E, Huber P, et al. Primary colonic lymphoma. J Surg Oncol. 2000;74(4):257–62.
98. Yu H, Wang Y, Peng L, Lia A, Zhang Y. Endoscopic manifestations of primary colorectal lymphoma. Hepato-Gastroenterology. 2014;61(129):76–8.
99. Mendelson RM, Fermoyle S. Primary gastrointestinal lymphomas: a radiological-pathological review. Part 1: stomach, oesophagus and colon. Australas Radiol. 2005;49(5):353–64.
100. Koniaris LG, Drugas G, Katzman PJ, Salloum R. Management of gastrointestinal lymphoma. J Am Coll Surg. 2003;197(1):127–41.
101. Maddocks K, Blum KA. Treatment strategies in mantle cell lymphoma. Cancer Treat Res. 2015;165:251–70.
102. Stanojevic GZ, Nestorovic MD, Brankovic BR, Stojanovic MP, Jovanovic MM, Radojkovic MD. Primary colorectal lymphoma: an overview. World J Gastrointest Oncol. 2011;3(1):14–8.
103. Ghimire P, Wu GY, Zhu L. Primary gastrointestinal lymphoma. World J Gastroenterol. 2011;17:697–707.
104. Arora N, Manipadam MT, Pulimood A, Ramakrishna BS, Chacko A, Kurian SS, et al. Gastrointestinal lymphomas: pattern of distribution and histological subtypes: 10 years experience in a tertiary centre in South India. Indian J Pathol Microbiol. 2011;54(4):712–9.
105. Vetro C, Romano A, Amico I, Conticello C, Motta G, Figuera A, et al. Endoscopic features of gastro-intestinal lymphomas: from diagnosis to follow-up. World J Gastroenterol. 2014;20(36):12993–3005.
106. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. Blood. 2006;107:265–76.
107. Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116:3724–34.
108. Warrick J, Luo J, Robirds D, Branson J, Frater JL, Kreisel F, et al. Gastrointestinal lymphomas in a North American population: clinicopathologic features from one major Central-Midwestern United States tertiary care medical center. Diagn Pathol. 2012;28(7):76.
109. Ekstrom-Smedby K. Epidemiology and etiology of Non-Hodgkin lymphoma: a review. Acta Oncol. 2006;45:258–71.
110. Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood. 2004;104:1258–65.
111. Aschebrook-Kilfoy B, Caces DB, Ollberding NJ, Smith SM, Chiu BC. An upward trend in the age-specific incidence patterns for mantle cell lymphoma in the USA. Leuk Lymphoma. 2013;54(8):1677–83.
112. Romaguera JE, Medeiros LJ, Hagemeister FB, Fayad LE, Rodriguez MA, Pro B, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. Cancer. 2003;97:586–91.
113. Salar A, Juanpere N, Bellosillo B, Domingo-Domenech E, Espinet B, Seoane A, et al. Gastrointestinal involvement in mantle cell lymphoma: a prospective clinic, endoscopic, and pathologic study. Am J Surg Pathol. 2006;30:1274–80.
114. Ruskoné-Fourmestraux A, Delmer A, Lavergne A, Molina T, Brousse N, Audouin J, et al. Multiple lymphomatous polyposis of the gastrointestinal tract: prospective clinicopathologic study of 31 cases. Groupe D'étude des Lymphomes Digestifs. Gastroenterology. 1997;112(1):7–16.
115. Leoncini L, et al. Burkitt lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC; 2008. p. 262–4.
116. Hartge P, Wang S. Overview of the etiology and epidemiology of lymphoma. In: Mauch PMAJOCB, Dalla-Favera R, Harris NL, editors. Non-Hodgkin's lymphomas. New York: Lippincott, Williams andWilkins; 2004. p. 711–27.
117. Vianna NJ. The malignant lymphomas: epidemiology and related aspects. Pathobiology Annual. 1977;7:231–55.
118. Raphael M, Said J, Borisch B, Cesarman E, Harris NL. Lymphomas associated with HIV infection. In: Swerdlow SH, Campo E, HarrisNL JES, Pileri SA, Stein H, et al., editors. WHO classification oftumors of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARCPress; 2008. p. 340–1.
119. Oyama T, Ichimura K, Suzuki R, Suzumiya J, Ohshima K, Yatabe Y, et al. Senile EBV+ B-cell lymphoproliferative disorders: a clin-icopathologic study of 22 patients. Am J Surg Pathol. 2003;27(1):16–26.
120. De Vita S, Sacco C, Sansonno D, Gloghini A, Dammacco F, Crovatto M, et al. Characterization of overt B-cell lymphomas in patients withhepatitis C virus infection. Blood. 1997;90(2):776–82.
121. Wu W, Doan N, Said J, Karunasiri D, Pullarkat ST. Strong expression of chemokine receptor CCR9 in diffuse large B-cell lymphoma and follicular lymphoma strongly correlates with gastrointestinal involvement. Hum Pathol. 2014;45(7):1451–8.
122. Ma S. Risk Factors of Follicular Lymphoma. Expert Opin Med Diagn. 2012;6(4):323–33.
123. De Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol. 2008;6:451–8.
124. Bertoni F, Rinaldi A, Zucca E, Cavalli F. Update on the molecular biology of mantle cell lymphoma. Hematol Oncol. 2006;24:22–7.
125. Orem J, Mbidde EK, Lambert B, de Sanjose S, Weiderpass E. Burkitt's lymphoma in Africa, a review of the epidemiology and etiology. Afr Health Sci. 2007;7(3):166–75.
126. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v116–25.
127. Scott DW, Wright GW, Williams PM, Lih CJ, Walsh W, Jaffe ES, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. Blood. 2014;123:1214–7.
128. Akasaka T, Lossos IS, Levy R. BCL6 gene translocation in follicular lymphoma: a harbinger of eventual transformation to diffuse aggressive lymphoma. Blood. 2003;102:1443.
129. Dreyling M, Ghielmini M, Marcus R, Salles G, Vitolo U, Ladetto M, ESMO Guidelines Working Group. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii76–82.
130. Vose JM. Mantle cell lymphoma: 2015 update on diagnosis, risk-stratification, and clinical management. Am J Hematol. 2015;90(8):739–45.
131. Fernàndez V, Salamero O, Espinet B, Solé F, Royo C, Navarro A, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res. 2010;70:1408–18.
132. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin lymphoma staging classification. Cancer Res. 1971;31(11):1860–1.

133. Martelli M, Ferreri AJ, Agostinelli C, Di Rocco A, Pfreundschuh M, Pileri SA. Diffuse large B-cell lymphoma. Crit Rev Oncol Hematol. 2013;87(2):146–71.
134. Cheson BD. Role of functional imaging in the management of lym-phoma. J Clin Oncol. 2011;29(14):1844–54.
135. Miller TP. The limits of limited stage lymphoma. J Clin Oncol. 2004;22(15):2982–4.
136. Dunleavy K, Pittaluga S, Czuczman MS, Dave SS, Wright G, Grant N, et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. Blood. 2009;113:6069–76.
137. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, Pileri SA, Malik F, Macon WR, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. Cancer. 2011;117:5058–66.
138. Van Oers MH, Klasa R, Marcus RE, Wolf M, Kimby E, Gascoyne RD, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood. 2006;108:3295–301.
139. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, et al. A new prognostic index (MIPI) for patients with advanced mantle cell lymphoma. Blood. 2008;111:558–65.
140. Rummel M, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, muticentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381:1203–10.
141. Romaguera JE, Fayad L, Rodriguez MA, Broglio KR, Hagemeister FB, Pro B, et al. High rate of durable remission after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus Hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol. 2005;23:7013–23.
142. Wang L, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibruitinib in relapsed or refractory mantle cell lymphoma. N Engl J Med. 2014;369:507–16.
143. Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, Cortes J, Garcia-Manero G, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006;106(7):1569–80.

Palliative Care in the Patient with Gastrointestinal Malignancies

20

David J. Debono

Introduction

There has been considerable progress in the management of gastrointestinal (GI) malignancies in the last 2 decades. Improved adjuvant systemic therapy in colorectal cancer has increased the cure rate in lymph node-positive disease. Chemotherapy and biological therapies have significantly prolonged life in metastatic colon cancer: altering the disease course to one of a chronic disease often for a period of years. Improved adjuvant and neoadjuvant therapies in esophageal and gastric cancer have led to longer life in these diseases. Finally, modern chemotherapy regimens have been shown to prolong survival in patients with metastatic pancreatic cancer who have adequate performance status.

However, despite these advances, many patients present with metastatic or develop recurrence of their cancer after curative intent therapy. In nearly all of these patients, cure of disease is not possible. These patients are destined to die of their disease. There are numerous clinical questions that arise in the management of these patients. The intent of this chapter is to try to address some of these questions and to provide some guidance in how we communicate with patients and families as they suffer through relapses of their disease or enter the end of their lives.

Section 1: Invasive Palliative Interventions

Esophageal Stenting in Esophageal Cancer

The most troubling symptom for patients with esophageal cancer is dysphagia. This is often the symptom that brings patients to medical attention. The optimal management of patients is dependent on the degree of esophageal obstruction, the presence or absence of disseminated metastatic disease, the degree of performance status decline, and the nutritional needs of the patient.

In patients with significant dysphagia, attempts at reestablishing swallowing function are appropriate. In patients with localized disease, definitive surgery is recommended followed by concurrent chemotherapy/radiation [1]. In the nonoperative patient, treatment options include esophageal dilation, self-expanding metal stents, radiation therapy via external beam therapy or brachytherapy, or concurrent chemotherapy/radiation.

The management of dysphagia in advanced esophageal cancer has been the subject of a systematic review [2]. The authors reviewed 53 studies involving nearly 4000 patients. They noted that rigid plastic stents, esophageal dilation, and thermal or chemical ablative therapies are not recommended due to high risk of recurrent dysphagia and/or delayed complications. They did recommend self-expanding metal stent insertion: particularly antireflux stents and double-layered Nitinol stents. The newer double-layered stents were noted to be associated with longer survival and fewer complications [2]. High-dose brachytherapy has been compared to metal stent placement. Brachytherapy was associated with a slower relief of dysphagia but ultimately had better long-term relief of dysphagia with fewer complications [3]. However, brachytherapy has not been widely accepted due to lack of widespread availability of this technology. A randomized trial of self-expanding stent with or without external beam radiation is underway in the United Kingdom [4]. It is hoped that immediate external beam radiation after stent placement will diminish the need for reintervention for tumor regrowth or hemorrhage.

Until we have results from modern randomized trials, the use of self-expanding metal stents (preferably double-layered and/or antireflux) or brachytherapy are the preferred procedures to alleviate dysphagia in nonoperative patients [2]. Stenting is associated with a more rapid return of swallowing function.

D. J. Debono (✉)
Oncology and Palliative Care Solutions, Anthem Inc., Bloomfield Hills, MI, USA
e-mail: david.debono@anthem.com

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_20

Palliative Gastrectomy in Advanced Gastric Cancer

Patients with gastric cancer often appear to have localized disease at the time of original staging. These patients, if they have adequate performance status, are taken to surgery for definitive resection. However, it is not unusual for disseminated intra-abdominal disease to be detected at the time of surgery. A clinical question has been posed in these patients: Should they be considered for palliative intent gastrectomy?

This has been the subject of numerous articles, none of which were randomized controlled trials. In one study, Yang and colleagues reported on 267 patients taken to laparotomy for apparent localized gastric cancer [5]. This group of 267 patients all had peritoneal disease at the time of surgery. Patients underwent gastrectomy if there was no involvement of the root of the mesentery, no involvement of major vessels, no infiltration of adjacent organs such as common bile duct, pancreas, duodenum, or esophagus, and no fixation of the tumor [5]. There were 114 patients in the resection group and 153 patients who did not undergo gastrectomy. Survival favored the resection group (median overall survival of 14 months vs. 8.57 months) [5]. Morbidities were higher in the resection group, but treatment-related mortality was no different. In patients with "P3" disease (numerous metastases to distant peritoneum), there was no advantage to the gastrectomy [5].

This question has also been the topic of a meta-analysis. The authors assessed 3000 patients across 14 studies of patients with advanced gastric cancer [6]. These studies included patients with T4 disease, N3 disease, and M1 disease. The results again favored the group that underwent gastrectomy versus the group that did not undergo gastrectomy with regard to overall survival [6]. The study demonstrated an advantage for patients with peritoneal metastases, liver metastases, or distant lymph node disease. Survival was particularly favorable in patients who underwent surgery and postoperative chemotherapy [6].

Investigators in Japan and Korea have reported plans for a randomized controlled trial of palliative gastrectomy versus nonoperative management in patients with incurable gastric cancer [7]. Until data from this study are available, the role of palliative gastrectomy in the setting of incurable gastric cancer remains unknown. The current National Comprehensive Cancer Network (NCCN) guidelines do not recommend gastrectomy for patients with peritoneal seeding or distant metastatic disease [8]. At this time, it is reasonable to consider palliative surgery in a patient with a good functional status, limited metastatic disease, local symptoms, and who is also a candidate for postoperative chemotherapy [6].

Management of Malignant Bowel Obstruction

Malignant bowel obstruction (MBO) is defined as obstruction of either small or large bowel due to effects of advanced intra-abdominal malignancy. Malignant bowel obstruction is particularly common in gastrointestinal malignancies with an incidence as high as 28% [9]. Obstruction can be due to direct obstruction from malignant peritoneal implants or due to malignant adhesions. Other potential causes include benign adhesions (most patients have already had an abdominal surgery in the past), incarcerated hernia, volvulus, severe constipation, or a second intra-abdominal malignancy. Cancers commonly associated with malignant bowel obstruction include ovarian, gastric, colorectal, and pancreas.

The initial question that arises when a patient presents with abdominal pain, abdominal distention, or intractable nausea/vomiting is whether the patient is suffering from an MBO. Initial evaluation includes plain abdominal radiographs and a surgical consultation. In nonemergent cases, a computed tomography (CT) scan of the abdomen and pelvis is often utilized to clarify whether peritoneal carcinomatosis is present and whether there is evidence of a single versus multiple points of obstruction. The presence of fecal stasis can also be ascertained.

If indeed MBO is diagnosed, one faces a very difficult clinical question. Is there a role for surgery to manage this obstruction? This question has been discussed in numerous studies that are typically nonrandomized, retrospective studies—often involving single institutions. The question has been the topic of 2 major systematic reviews.

Kucukmetin and colleagues published a Cochrane Database Review on the subject of palliative surgery versus medical management in the setting of malignant bowel obstruction from advanced ovarian cancer [10]. They found no randomized trials comparing surgical management to medical management. They identified a single nonrandomized study of 47 patients being assigned either octreotide therapy or surgical management. Patients assigned to surgical management had longer overall survival, but quality-of-life assessments and other measures were not reported [10].

Olson et al. performed a systematic review of palliative surgery for MBO from carcinomatosis [9]. After reviewing 3158 articles, they identified 18 articles involving 868 patients that fit their inclusion criteria. Validated quality-of-life metrics were not available in any of the studies. Markers of quality of end-of-life care were also not reported (goals of care meeting, advance care planning sessions, etc.). Generally, surgery was associated with an improvement in obstructive symptoms, ability to tolerate an oral diet, and ability to be discharged home. However, there was significant morbidity and mortality. Thirty-day mortality ranged from 6% to 32%, and serious postoperative complications

ranged from 7% to 44%. Recurrent obstruction was seen in 6–47% of patients, and only 32–71% of patients tolerated an oral diet at 60 days. Repeat surgery was uncommon (2–15%), but in patients who did undergo additional surgery, only 46% returned home [9]. The overall survival time for this group of patients is generally poor. In their study, Olson reported that median survival after MBO ranged from 26 to 273 days [9]. Patients without ascites or palpable masses who underwent surgery and had return of bowel function had a median survival time of 154–192 days. However, patients with ascites, palpable masses, or lack of return of bowel function survived just 26–36 days. The other troubling feature of MBO that was outlined by Olson was that often the majority of a patient's remaining life is spent in the hospital [9].

The decision regarding surgical intervention is a difficult one that often relies on clinical intuition. Henry and colleagues reviewed their single-institution experience of 523 patients with malignant bowel obstruction in hopes of identifying risk factors that might guide decision-making. [11] They were able to identify 5 risk factors that helped predict 30-day mortality. Carcinomatosis, ascites, complete small bowel obstruction, hypoalbuminemia, and abnormal white blood cell count each were independently predictive of 30-day mortality. In their nomogram, 30-day mortality was 9% if the patient had zero risk factors and increased steadily to 69% if the patient had 5 risk factors. They note that patients with 4 or 5 risk factors should rarely be offered surgery [11].

They then developed another nomogram to predict 30-day mortality in relation to whether the patient had surgery or not. They found 4 risk factors that helped stratify patients. These 4 factors were carcinomatosis, leukocytosis, normal albumin, and nongynecologic cancer. Patients with zero risk factors had a 10% 30-day mortality if they underwent surgery versus 40% mortality if the patient did not undergo surgery. This is in stark contrast to the patients with 4 risk factors where the surgical 30-day mortality was 70% versus 15% for those patients who did not have surgery. Again, the authors suggested that patients with scores of 3 or 4 should rarely be offered surgery. The authors offer a strategy using both nomograms that can help guide this difficult decision of whether to offer surgical intervention (Fig. 20.1) [11].

The other large question that comes to mind in these patients is what nonoperative options exist for patients who are not felt to be surgical candidates? There are medical options for patients as well as palliative interventions. The medical treatment of MBO centers on 3 drugs: (1) octreotide, (2) dexamethasone, and (3) ranitidine [12]. Octreotide is a somatostatin analog and is felt to exert its palliative benefit by diminishing intestinal and gastric secretion so that nausea and vomiting diminish and quality of life improves. Dexamethasone's mechanism of action is poorly understood but likely decreases inflammation at the site of obstruction and can help delay or decrease obstructive symptoms. Finally, ranitidine is a commonly used histamine-2 blocker that can diminish gastric secretions.

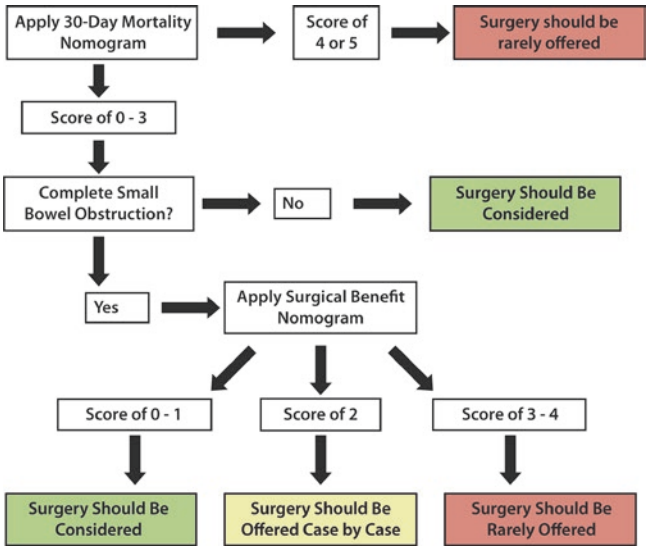


Fig. 20.1 An algorithm for scoring patients with malignant bowel obstruction. (Reprinted with permission from Henry et al. [11])

Octreotide has been the subject of numerous randomized clinical trials. These trials have been hampered by small size and variable primary endpoints. Some studies use short-acting octreotide, while others use depot formulations. In a recent trial, octreotide was compared to scopolamine butylbromide in the setting of MBO in ovarian cancer [13]. Octreotide was shown to decrease gastric secretions and also decrease the number of emetic episodes and intensity of nausea [13]. In another recent randomized, double-blind study of octreotide versus placebo, octreotide was no different than placebo in the primary endpoint of days free of vomiting [14]. However, in a multivariate analysis, octreotide was shown to decrease the number of emesis episodes [14]. Thus, the data are mixed on whether octreotide alters the natural history of MBO. However, in recently published guidelines, it is recommended that octreotide be considered for the treatment of MBO with peritoneal carcinomatosis [12].

The use of corticosteroids has also been the subject of investigation in the management of MBO. Though its mechanism of action is unclear, a Cochrane review of 10 randomized clinical trials of glucocorticoids was performed [15]. Of these 10 trials, 3 were unpublished at the time of the review. There was no difference in 1-month mortality. There was a trend in favor of corticosteroids (dose range of 6–16 mg/day of dexamethasone) in helping to resolve obstructive symptoms, and they note that the number to treat was 6 (treat 6 patients to resolve 1 obstruction). No serious toxicity was detected in this short-term use, though not all studies provided detailed toxicity data [15].

Finally, the role of histamine 2 antagonists and proton pump inhibitors has also been the subject of clinical trials and meta-analysis. The meta-analysis by Clark et al. evaluated 7 clinical trials looking at gastric volume aspirates in the setting of MBO [16]. Their analysis suggested that ranitidine was a superior agent in decreasing gastric volume output, and the authors felt that ranitidine should be included in the medical management of MBO [16]. Recent published guidelines, however, favor proton pump inhibitors given intravenously [12].

In patients who are not felt to be surgical candidates, a common clinical question is whether or not a palliative venting percutaneous endoscopically placed gastrostomy (PEG) tube should be placed. A venting PEG tube has the potential of venting gastric contents, which can successfully eliminate nausea and vomiting in the nonoperable patient, and allow for a home discharge without a nasogastric tube. There are no set criteria in selecting patients for PEG placement; however, recent guidelines note that venting gastrostomies are often placed very late in the disease course [12]. In single-institution studies, the success rate of venting gastrostomy tubes in eliminating the need for nasogastric tubes and alleviating nausea and vomiting is as high as 96% [17]. A general recommendation is to place a venting PEG tube if medical management is not successful in alleviating the obstruction after a period of 3–7 days [12]. In a patient with malignant ascites, it is recommended that the ascites be drained prior to venting gastrostomy [12]. Ascites drainage can be accomplished via paracentesis; however, a large single-institution series demonstrated that patients could safely and successfully have both an indwelling peritoneal catheter for ascites drainage along with a venting gastrostomy [18].

Section 2: Pearls of Pain Management in the Gastrointestinal Oncology Patient

Celiac Plexus Blocks for Pancreatic Cancer

Pain is nearly universal in patients diagnosed with pancreatic cancer. Though a small minority are candidates for curative-intent resection, the vast majority of patients are unresectable at the time of diagnosis. Patients whose disease is unresectable often have upper abdominal pain as a result of local growth of their tumor. Patients who undergo curative-intent surgery remain at risk for local recurrence of their disease, and these patients can also develop upper abdominal and back pain. It is in these patients that celiac plexus block is often considered. Despite being first described in 1914, the role of celiac plexus block remains controversial today.

Pain associated with pancreatic cancer is poorly understood. It is felt to directly involve the celiac nerve plexus, which transmits visceral pain signals from the upper abdomen including the region of the pancreas. Other causes of pain may be neuropathic pain from invasion of the celiac plexus, infiltration of peripancreatic nerves, chronic pancreatic ductal obstruction, and invasion of local structures and organs. Celiac plexus neurolysis using ethanol is felt to disrupt afferent pain impulses resulting in nerve fiber demyelination and axonal degeneration [19]. The first randomized trial demonstrating an advantage for celiac plexus neurolysis was published in 1993 by Lillemoe and colleagues [20]. This was a randomized, double-blind, placebo-controlled trial of 140 patients undergoing surgery for pancreatic cancer but found to have unresectable disease. The patients were randomized to receive chemical celiac plexus neurolysis with 50% alcohol or placebo injection with saline. Mean pain scores favored the neurolysis group at 2 months, 4 months, and 6 months postoperatively [20].

In 2015, Lavu and colleagues published their large, prospective, randomized double-blind study of ethanol celiac plexus neurolysis in patients who underwent exploration for what was felt to be resectable pancreatic and periampullary adenocarcinoma [19]. They randomized 400 patients with resected pancreatic/periampullary carcinoma to celiac plexus neurolysis or placebo. They were unable to demonstrate an advantage in subsequent pain scores in patients receiving intraoperative neurolysis [19]. Though this was a large and well-conducted study, their pain evaluation survey return rate markedly diminished over time, making it a difficult study to interpret [19]. Nevertheless, this study calls into question the practice of immediate, intraoperative celiac plexus neurolysis in patients with resectable pancreatic cancer.

Finally, in 2013, a systematic meta-analysis was published assessing the value of percutaneous celiac plexus neurolysis in pain associated with pancreatic cancer [21]. They reviewed 102 studies, and only 6 fulfilled their criteria involving 358 patients. They found improved pain scores at 4 weeks and 8 weeks and less opioid consumption. Thus, this analysis favored celiac plexus neurolysis in patients with pain associated with pancreatic cancer [21].

The evidence for the efficacy of celiac plexus neurolysis is mixed. The primary management of pain associated with pancreatic cancer should be opioid therapy. In patients with uncontrolled pain, a celiac plexus neurolytic block is very reasonable as second-line therapy and is encouraged.

Pain Assessment and Management

The control of pain is an important part of managing the patient with advanced GI malignancies. Pain can be due to the effects of the disease or from toxicity of treatment. Patients can experience nociceptive pain due to pain involv-

ing bone metastases or soft-tissue sites of disease. There can also be neuropathic pain, which can be due to local effects of either primary or metastatic tumors such as involvement of the celiac axis in primary pancreatic cancer or pelvic neuraxial involvement from locally recurrent rectal cancer. Neuropathic pain is also commonly seen as a result of chemotherapy: particularly due to cisplatin, carboplatin, and oxaliplatin as well as the taxanes.

Initial pain management involves an initial comprehensive pain assessment. This will provide baseline information on the character of the pain, the severity of the pain, and the potential causes. There are specific cancer pain syndromes that are important to recognize. These include pain involving metastatic disease to the spine, which might signify early spinal cord compression; abdominal pain due to malignant bowel obstruction; sacral plexus involvement from pelvic recurrence of disease; celiac plexus involvement from primary or metastatic disease; and other syndromes such as intercostal nerve involvement from metastatic disease to ribs/pleura. Recognition of these syndromes will often lead to specific interventions.

Options for management of pain are numerous. Radiation therapy is typically part of the initial plan in patients with localized osseous metastatic disease. Paracentesis is commonly needed in managing pain in the patient with intra-abdominal dissemination of their disease. In a patient with malignant bowel obstruction, nasogastric tube suction and medical interventions such as somatostatin analogs and corticosteroids can specifically improve the pain seen in these patients [12].

The most common intervention for patients with pain related to metastatic disease is the initiation of opioid therapy. Opioid therapy has been extensively reviewed [22–24]. Agents most commonly used include morphine, hydromorphone, oxycodone, hydrocodone, transdermal or transmucosal fentanyl, and methadone. The pharmacology and pharmacokinetics of these drugs have important differences. In patients with advanced GI malignancies, there is often renal and/or hepatic compromise, making an understanding of opioid pharmacology important.

Morphine and hydromorphone are metabolized via glucuronidation in the liver: a process that is reasonably well-preserved in hepatic dysfunction [25]. Hydrocodone is metabolized by the cytochrome p450 enzyme CYP2D6 [26]. Fentanyl is metabolized by the cytochrome p450 enzyme CYP3A4 as are oxycodone and methadone [26]. Methadone is also metabolized by cytochrome p450 enzymes CYP2D6 and 2B6, but is also variably metabolized by CYP2C8, 2C19, 2D6, and 2C9 [26].

Opioids metabolized by the cytochrome p450 system are particularly prone to drug–drug interactions. Interactions with enzyme inducers lead to lower opioid blood levels, enzyme inhibitors lead to higher opioid blood levels, and competitive inhibition from drugs that are substrates of p450 enzymes can also lead to higher opioid levels.

In the presence of renal insufficiency, it is recommended that drugs that are primarily cleared hepatically be utilized cautiously: such as fentanyl, oxycodone, or methadone. In the presence of hepatic insufficiency, careful use of morphine or hydromorphone is recommended. In the presence of both renal and hepatic dysfunction, an earnest effort to establish the goals of care should be outlined. Choice of opioids should be made based on the relative severity of the renal and hepatic dysfunction—choosing an opioid accordingly and beginning at a low dose. The patient needs to be followed closely and the dose carefully titrated.

Intrathecal Infusion Pumps

Despite advanced surgical techniques, improved radiation technology, and evolving chemotherapy strategies for many GI malignancies, there remain patients who develop intractable pain. Usually these pain syndromes are related to metastatic disease involving the abdomen, the retroperitoneum, or the pelvis. Pelvic recurrences are particularly problematic—especially in patients with cancer of the rectum. Patients with cancers of the upper abdomen, such as pancreatic cancer and gastric cancer, may develop severe pain syndromes related to disease involving the celiac plexus. The character of pain in these syndromes is variable, but often patients express a feeling of ongoing, gnawing pain. The pain in these patients is often a combination of neuropathic and nociceptive pain. The management of these pain syndromes can be particularly challenging.

The initial management plan of patients with these pain syndromes should revolve around the oral or transdermal administration of opioids with drugs such as morphine, oxycodone, methadone, hydromorphone, fentanyl, or hydrocodone. However, dose escalation of these drugs is often met with significant toxicity—particularly central nervous system (CNS) toxicity including myoclonus or sedation. Patients who are unable to tolerate adequate doses of these agents to control their pain may be candidates for more invasive interventions, such as intrathecal infusion pumps. Also, there are patients where the neuropathic component of their pain predominates, and this pain is often incompletely responsive to oral or transdermal opioids. Again, in these patients, intrathecal infusions can be quite helpful.

Intrathecal administration of opioids, local anesthetics, and adjunct drugs such as clonidine has been increasingly utilized in patients with intractable, cancer-related pain. The feasibility of this technique is dependent on the availability of this technology and skilled practitioners in a medical community. It is important for the practicing oncologist to identify colleagues in their local community who have access to

intrathecal infusion devices, and who are skilled in their insertion and their maintenance.

The intrathecal infusion of morphine in refractory cancer pain has been the subject of a large randomized controlled trial. Smith and colleagues randomized 202 patients who had persistent pain despite 200 mg of oral morphine equivalent/day or who had pain and intolerance to adequate systemic doses of opioids. The patients were randomized to continued medical management of their pain versus the intrathecal infusion of morphine. Both groups had dose titration. The study's primary endpoint was a 20% decrease in the visual analog pain score (VAS). Clinical success was defined as either a 20% decrease in VAS scores or equal VAS but a 20% or greater decrease in opioid toxicity 4 weeks after randomization [27].

In patients randomized to the intrathecal administration of morphine, 84% of patients achieved clinical success versus 70% with continued medical management. Regarding efficacy, VAS scores with the intrathecal infusion fell 51% compared to 39% with continued medical management. The composite toxicity scores fell by 50% with intrathecal infusion versus 17% with continued medical management [27].

This randomized trial also assessed the survival of both groups of patients. At 6 months, the survival was 54% in the intrathecal infusion group versus 37% in the patients medically managed. The study had an additional analysis at 12 weeks, and pain and toxicity advantages for the intrathecal infusion remained [28]. Since some of the patients in the medical management group ultimately had intrathecal infusion pumps placed, the authors compared all patients who received an intrathecal infusion pump versus those who did not. Survival analysis again showed an advantage for all patients receiving an intrathecal infusion pump (approximately 50% 6-month survival) versus 32% 6-month survival in the medical management group. The survival analysis was not a planned analysis, and unrecognized confounding factors may have contributed to the differences [28]. Nevertheless, it remains an interesting observation that patients with superior pain relief and toxicity control may live longer.

The proper selection of cancer patients for intrathecal infusion and the appropriate management of cancer patients with intrathecal infusions have been reviewed [29], and guidelines have been published [30]. Important recommendations from the guideline include the following:

1. Patients should undergo a stepped approach to pain management before proceeding to intrathecal therapy.
2. Titration of intrathecal medications should be done slowly.
3. Formal pain assessment and quality-of-life measures should be part of the routine management of patients on intrathecal infusions.
4. Intrathecal infusion pumps should be shielded from radiation when possible, and interrogated after radiation to ensure ongoing function.
5. Intrathecal infusion pumps are generally not recommended for patients with epidural metastases.
6. A preimplantation psychological evaluation is recommended for patients with extended longevity who have developed a chronic pain syndrome.
7. A preimplantation trial of intrathecal or epidural opioid administration has been suggested and is mandatory for some insurance companies, but clinical trials on preimplantation intrathecal trials have not been convincing for benefit.
8. The need for anticoagulant therapy is not an absolute contraindication to intrathecal infusions; however, the appropriate management of anticoagulants is detailed in the guideline [30].

Section 3: Common Toxicities of Oxaliplatin and Irinotecan

Oxaliplatin-Induced Neurotoxicity

Platinum-induced neurotoxicity has been described since the first clinical experience with cisplatin. There are now second- (carboplatin) and third-generation (oxaliplatin) platinum drugs, and neurotoxicity remains an issue with each one of these. Oxaliplatin is a very important chemotherapeutic agent in the management of GI malignancies. It has also become a commonly used agent in the management of esophageal, gastric, and pancreatic cancer. Hematological toxicity is typically easily managed; however, the most important short-term and long-term toxicity is peripheral sensory neuropathy. The neurotoxicity of oxaliplatin has been the subject of intense investigation and is particularly important in colorectal cancer patients. Some have advocated that this side effect should be called chemotherapy-induced peripheral neurotoxicity to better reflect the fact that this clinical syndrome results from toxic effects of chemotherapy [31]. Adding oxaliplatin to fluoropyrimidine-based chemotherapy had a significant impact on the cure rate of stage III colorectal cancer and high-risk stage II colon cancer, and is often given repeatedly in patients with metastatic colorectal cancer. Hence, there are large numbers of patients who are receiving oxaliplatin in this common disease. This has heightened the importance of understanding this neurotoxicity, understanding its typical course, and attempting to both prevent this toxicity and treat it. Despite extensive clinical and animal studies, the exact pathophysiology of oxaliplatin-induced neurotoxicity is not known. Clinically, this neurotoxicity is manifest as numbness and tingling in distal extremities, cold sensitivity, paresthesias, diminished

vibratory sensation, loss of distal reflexes, and can even lead to loss of proprioception with an ataxic gait [31].

Oxaliplatin is felt to cause both an acute neurotoxicity and a chronic neurotoxicity. The acute neurotoxicity is characterized by cold sensitivity (touching cold objects or swallowing cold liquids), throat and peripheral dysesthesias, and muscle cramps. Chronic neurotoxicity is associated with a sensory neuropathy with numbness, tingling, and painful dysesthesias [32].

The clinical course of oxaliplatin neurotoxicity is variable, but there are now prospective data that have shed some light on the typical course that patients take. In their prospective study of 346 patients enrolled in a randomized study of intravenous (IV) calcium/magnesium for the prevention of oxaliplatin-induced neurotoxicity, Pachman assessed neurotoxicity before and after each cycle of FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) and then at 5 time points after completing FOLFOX chemotherapy [33]. Pachman reported that 89% of patients had at least 1 symptom of acute neuropathy with the first cycle of therapy, and these symptoms peaked by day 3 and then improved [33]. However, the symptoms did not predictably resolve between treatments. Acute neuropathy symptoms became worse during cycles 2 through 12, with the symptoms being described as moderate/severe twice as often during the later stages of therapy as compared to cycle 1 [33]. For chronic neurotoxicity, the most common symptom was tingling followed by numbness and pain [33]. During chemotherapy, hands were more commonly affected than feet, but at 18 months post chemotherapy, the feet were more commonly affected. The patients with the worst acute neurotoxicity during cycle 1 were the patients most likely to report chronic sensory neurotoxicity. Chronic neurotoxicity did improve after chemotherapy completion. However, at 18 months post chemotherapy, 19% of patients continued to report severe sensory neuropathy symptoms [33].

There have been numerous studies of agents to prevent platinum-induced neurotoxicity. These studies have been reviewed in a Cochrane review, [34] have been the subject of a comprehensive review article [32], and have also been outlined as part of the American Society of Clinical Oncology (ASCO) practice guidelines for the prevention and management of chemotherapy-induced peripheral neuropathy [35]. In all 3 of these documents, there was no intervention proven to prevent platinum-induced neuropathy. In fact, 2 trials (one with the calcium-channel blocker nimodipine and one with the supplement acetyl-L-carnitine) demonstrated worse neurotoxicity with the intervention [35].

There is one intervention that deserves special mention. The mechanism of the neurotoxicity of oxaliplatin has been proposed to be from the production of oxalate (from oxaliplatin metabolism), which subsequently chelates calcium and magnesium—elements important in the function of ion channels in neuronal membranes [36]. Thus, the administration of IV calcium and magnesium with FOLFOX chemotherapy was studied. In a retrospective study of 161 patients, Gamelin and colleagues reported that only 4% of patients discontinued oxaliplatin when given IV calcium and magnesium versus 31% of patients who did not receive calcium and magnesium [37]. This observation led to a significant change in practice patterns, with many oncologists adapting the use of IV calcium and magnesium. A randomized study of IV calcium and magnesium in adjuvant FOLFOX chemotherapy also showed promising results for diminishing chronic neuropathy; however, the study was stopped early when another study suggested that IV calcium and magnesium decreased chemotherapy efficacy (this detrimental effect was later shown to not be present) [38]. Thus with the question of safety and efficacy of IV calcium and magnesium still open, a large randomized study was performed by the North Central Cancer Treatment Group (NCCTG) and the Alliance for Clinical Trials in Oncology group.

In 2014, Loprinzi and colleagues reported their large, well-conducted, randomized, double-blind study that assessed the value of IV calcium and magnesium in the setting of adjuvant FOLFOX chemotherapy in stage II and III colon cancer. Patients were randomized to 3 groups. One group received IV calcium and magnesium before and after FOLFOX therapy, another received placebo before and after chemotherapy, and the third group received IV calcium and magnesium before chemotherapy and placebo after chemotherapy. The primary endpoint of the trial was the European Organisation for Research and Treatment of Cancer (EORTC)-developed assessment tool called the QLQ-CIPN20, which is a validated tool specifically designed for chemotherapy-induced peripheral neuropathy (CIPN). Their study of 353 patients convincingly revealed no measurable effect of IV calcium and magnesium with regard to acute neurotoxicity, chronic neurotoxicity, or time to neurotoxicity [36]. Thus, the use of IV calcium and magnesium to prevent oxaliplatin neurotoxicity cannot be recommended. Hence, there remain no known agents to prevent oxaliplatin-induced neurotoxicity.

The guideline published by ASCO did provide a moderate recommendation for the use of duloxetine for the treatment of chemotherapy-induced neurotoxicity. The authors also suggested that the use of tricyclic antidepressants, gabapentin, or a compounded gel of baclofen, amitriptyline, and ketamine could be tried based on the published experience in other neuropathies [35].

Irinotecan-Induced Diarrhea

Irinotecan has proven to be a valuable drug in the management of metastatic colon cancer and metastatic pancreatic

cancer, and is often used in the management of gastroesophageal cancers. Irinotecan has been associated with neutropenia, but this toxicity in most cases is simple to control. It is also associated with acute, early-onset diarrhea (occurring during the infusion or in the 24 hours after the infusion) and late-onset diarrhea (occurring more than 24 hours after the infusion). The acute, early-onset diarrhea is part of a cholinergic excess syndrome and is easily controlled with parenteral atropine and can often be prevented with the prophylactic use of atropine prior to the infusion.

Late-onset diarrhea from irinotecan is much more clinically significant, and can result in severe uncontrolled diarrhea, electrolyte imbalances, and the need for hospitalization. Understanding this syndrome and preventing late-onset diarrhea remain topics of intense investigation.

The metabolism of irinotecan is highly complex. Irinotecan is a pro-drug and undergoes carboxylesterase-mediated hydrolysis to form SN-38: a compound that is 100–1000 times as cytotoxic as irinotecan. This conversion occurs primarily in the liver. Irinotecan is also metabolized by the cytochrome p450 system, with oxidation by CYP3A4 being the predominant isoenzyme involved. This metabolism converts irinotecan into 2 metabolites: one of which can again be converted back to SN-38. SN-38 is then conjugated to an inactive and nontoxic conjugate: SN 38 glucuronide. This conjugation step is mediated by hepatic UGT1A1, UGT1A7, and extrahepatic UGT1A7. However, SN 38 glucuronide can be converted back to SN38 by bacterial ß(beta)-glucuronidase and SN38 and irinotecan can also undergo enterohepatic circulation. Therefore, there are at least 3 mechanisms to enhance SN-38 production and the potential for increased cytotoxicity. It is also worth noting that the plasma half-life of irinotecan is 14.6 hours, but the half-life of SN 38 is 28.5 hours [39].

The late-onset diarrhea of irinotecan is still not fully understood. It is felt to be due to direct intestinal mucosal damage due to SN38-induced cytotoxicity. Cytotoxic effects seen include injury to tight junction proteins claudin 1 and occludin, causing damage to the intestinal barrier resulting in bacterial translocation. The intestinal concentration of SN38 is enhanced by bacterial ß(beta)-glucuronidase and enterohepatic recycling [39].

This complex pharmacology makes predicting toxicity of irinotecan difficult, and the prevention of this toxicity has proven to be elusive. This issue is further complicated by the various doses and schedules that have been utilized with irinotecan, making treatment decisions in individual patients difficult.

Numerous studies have been performed testing various agents and strategies to prevent late-onset diarrhea. These studies have been reviewed [39]. Suffice it to say that none of the strategies have yet to be shown to convincingly prevent late-onset diarrhea. One novel strategy that will require further follow-up is inhibitor of bacterial ß(beta)-glucuronidase. Such inhibitors would be expected to decrease intestinal SN38 exposure. This class of drugs has shown promise in animal models, and clinical studies are awaited. Antibiotic therapy with neomycin has been studied in randomized trials and was shown to decrease grade 3 diarrhea, but increased grade 2 diarrhea, and no convincing decrease in overall late-onset diarrhea was observed [39].

Genetic polymorphism of UGT1A1 is also a topic of important investigation. This enzyme is important in the conjugation of SN38 to its more soluble conjugate, which can more easily be eliminated in bile and urine. The isoenzyme UGT1A1 is felt to be the main member of the UGT family involved in the conjugation of SN38. Polymorphisms have been observed in the number of TA repeats in the TATA box of the UGT1A1 promoter. The most common polymorphism seen ("wild type") has 6 repeats. The most common variant polymorphism has 7 repeats and has been named UGT1A1∗28 (or 7/7). This polymorphism has been associated with reduced gene expression and diminished enzyme activity resulting in lower SN38 metabolism [40]. Clinical studies subsequently revealed a correlation between UGT1A1∗28 and irinotecan toxicity—especially neutropenia [41].

This observation led the US Food and Drug Administration (FDA) to recommend a labeling change on irinotecan: recommending that all patients receiving irinotecan be checked for UGT1A1 polymorphisms. Patients found to be homozygous for the UGT1A1∗28 polymorphism were recommended to have at least 1 dose level reduction in irinotecan. However, clinical studies in general have seen the strongest correlation with neutropenia and UGT1A1∗28 and less correlation with diarrhea. Because UGT1A1 metabolism is just 1 part of the metabolic phenotype of irinotecan, there remains controversy over the routine testing of UGT1A1 polymorphisms in patients receiving irinotecan therapy [42].

In patients with late-onset diarrhea due to irinotecan, guidelines recommend aggressive rehydration and electrolyte replacement and aggressive use of antidiarrheals [43]. First-line therapy should include liberal use of loperamide. In patients with severe diarrhea and evidence of the "gastrointestinal syndrome" (severe diarrhea, nausea, vomiting, anorexia, and abdominal cramping), immediate use of antibiotics with a fluoroquinolone is recommended after obtaining stool for stool pathogens, *Clostridium difficile*, and leukocytes. In patients not responding to loperamide, short-acting octreotide is recommended with rapid dose escalation to as high a dose as 500 mcg TID. Finally, deodorized tincture of opium at a dose of 10–15 drops in water every 3–4 hours is another agent that is reasonable in refractory cases or camphorated tincture of opium at a dose of 5 ml very 3–4 hours [43].

Section 4: Communicating with Patients Who Have Gastrointestinal Malignancies

Depression in the Patient with Gastrointestinal Malignancies

Depression has been shown to be a common comorbidity in patients with GI malignancies, particularly those with advanced disease. For example, it has been described that diagnostic criteria for depression are found in a significant percentage of patients with pancreatic cancer [44]. In a small, provocative study, Sebti reported that depression was a specific prodrome to the diagnosis of pancreatic cancer [45]. In their study of 15 patients with a recent diagnosis of pancreatic cancer, 10 patients were diagnosed with depression in the year prior to the diagnosis of pancreatic cancer [45]. This suggests the possibility of malignancy-related biological pathways that may result in depressive symptoms. In another study of pancreatic cancer patients, Breitbart noted that depression was associated with elevated levels of the proinflammatory cytokine IL-6 [46].

These studies begin to tell the story that the experience of advanced cancer can certainly have emotional and psychological effects, but the cancer itself may also have biological effects: both leading to a higher risk of depression. These studies and others have begun to emphasize the importance of identifying depression in oncology patients. This has led ASCO to publish guidelines on the screening, assessment, and care of anxiety and depressive symptoms in adults with cancer [47]. This guideline was adapted from Canadian guidelines previously published.

In their guideline, Andersen et al. noted that the first step in assessment for depression is identifying pertinent history and risk factors for depression and/or anxiety [47]. These include a personal history of depressive disorder, family history of depression, other psychiatric disorders including substance abuse, suboptimal social support, lower socioeconomic status, other chronic illnesses, and progressive cancer. This is followed by 2 questions from the 9-item Personal Health Questionnaire (PHQ-9) [48]:

1. Do you have little interest or pleasure in doing things?
2. Are you feeling down, depressed, or helpless?

If the patient scores a 0 or 1 on this screen, then no further screening is indicated. For patients scoring a 2 or 3 on either of these questions, they should complete the other 7 items on the PHQ-9. This will categorize patients as having mild, moderate, or severe symptomatology. Identifying those patients in the moderate or severe category then should lead to specific interventions [47].

The importance of identifying depressive and anxiety disorders goes beyond correcting symptoms. It is believed that successful treatment of these conditions can lead to better oncological outcomes. In a large population-based study of 24,000 patients with pancreatic cancer, 8% also carried the diagnosis of depression [49]. When evaluating outcomes, it was shown that overall survival, reception of curative surgery, and reception of appropriate chemotherapy were all negatively impacted by the presence of depression [49]. This correlation has also been demonstrated in men with localized prostate cancer. In a study of 41,000 men with prostate cancer, 1900 men also carried the diagnosis of depression [50]. The presence of depression correlated with less curative intent prostate surgery, and worse overall survival [50].

The take-home message regarding depression is that all oncology practices should begin to build routine depression screenings and assessments into their clinic work-flow. Oncology clinicians should also identify local resources and expertise in the fields of psychology and psychiatry. Though oncology practitioners may be able to manage uncomplicated depression, more complicated patients should be promptly referred to expert local providers.

Prognostic Awareness in the Patient with Gastrointestinal Cancers

The diagnosis of various gastrointestinal cancers carries equally variable prognoses. The diagnosis of stage I colon cancer carries an operative cure rate of 90% versus an operative cure rate of 50% in stage III disease. In esophageal cancer, many patients present with incurable disease at the time of diagnosis and have median survival of 10–15 months. For those who are candidates for curative intent therapy, the cure rate with combined modality therapy remains only approximately 35%. In pancreatic cancer, some patients present with localized disease and are candidates for curative intent surgery. However, surgery accomplishes cure in just 10–20% of patients.

When patients present to the oncologist or the multidisciplinary team with a new diagnosis of gastrointestinal cancer, the physicians assess the stage of disease, ensure appropriate pathological evaluation of biopsy material, and establish the optimal treatment strategy. Patients at these initial visits are often focused on achieving good outcomes, and they want their physicians to offer an honest assessment of their disease but also provide hope for the future. It is in these conversations that initial seeds of an honest appraisal of prognosis can be planted.

Over the course of a patient's illness, their prognosis can change as the disease changes. For example, a patient with localized pancreatic cancer agrees to surgery in hopes of

achieving a surgical cure despite the likelihood of cure being quite low. If the disease recurs, their disease is now incurable. However, multiagent chemotherapy has been shown to extend survival so immediate short-term survival might be favorable and frank discussion about prognosis might be deferred or delayed by either the patient or the clinician. This section outlines an approach to cultivating prognostic awareness over the course of a patient's illness.

An influential paper by Weeks detailed patient's understanding of prognosis in the setting of advanced and incurable lung or colorectal cancer [51]. Patients were interviewed and asked to articulate what the goal of their chemotherapy was. Surprisingly, 70% of lung cancer patients and 80% of colorectal cancer patients were unable to exhibit understanding that chemotherapy was not at all likely to cure their cancer [51]. Their results illustrate the difficulty in helping patients and families to understand prognosis and clearly show that new and different strategies are required to communicate prognosis honestly and effectively.

Prognostic awareness has been defined as the patient's capacity to understand their prognosis and the likely illness trajectory [52]. Prognostic awareness involves not just understanding the expected survival time or chance of cure of the disease, but also having a grasp of the expected natural history of the disease and the potential complications and symptoms of the disease. Prognostic awareness is important for a number of reasons. Having a good understanding of prognosis and natural history of the disease can allow patients to plan their lives—particularly when short-term survival is impaired. Prognostic awareness has also been shown to influence the care that patients receive near the end of their lives: Accurate prognostic awareness has been associated with less chemotherapy, less resuscitation measures, and earlier hospice enrollment near the end of life [53, 54].

However, explaining prognosis accurately involves conversations that are challenging, are often met with resistance from patients and families, often result in complex emotions, and may require a series of clinical encounters. Jackson and colleagues have suggested a 4-step process to help cultivate prognostic awareness [52]. In outlining their strategy, they note that this is a process that may take several visits to execute.

Part of the initial steps toward prognostic awareness is for the clinician to obtain the necessary information (from laboratory values, radiographic studies, and from expert colleagues) so that one can outline the expected natural history of the disease and the expected prognosis to the patient and family [52].

Once the clinician understands the prognosis, Jackson and colleagues recommend a 4-step process to cultivate prognostic awareness:

1. *The first step is an assessment of the patient's current prognostic awareness*. They suggest open-ended questions, such as "What's your sense of how you are doing?" or "How worried are you about what is going on right now?" This initial step will give the clinician an idea of how ready the patient is to discuss prognosis more frankly [52].
2. *The second step is to inquire whether the patient can imagine a poorer health state* [52]. Comment like "I know we are hoping that the chemotherapy provides a response in your tumor, but do you ever imagine what it would be like if things don't go well?" Or a question such as "What would it be like if you get sicker?" This technique is a useful way for the clinician to help the patient and family imagine what the future might look like, without letting go of their current level of hope [52].
3. *The third step is for the clinician to judge how ready the patient may be to discuss prognosis, and at the same time, determine the clinical urgency*. [52] Sometimes the patient explicitly asks detailed questions about their prognosis. It is the clinician's responsibility to deliver that information in a culturally sensitive way. Sometimes a patient may ask, "How do you think I am doing, Doctor?" A way of investigating what their awareness of their condition is to answer with the question, "I've noticed that you are getting weaker and not doing your usual activities. What is ***your*** body telling you?" [52].

Some patients are clinically stable and really are not prepared to discuss prognosis. In those patients, the conversation about prognosis should be deferred to a later visit. Though sometimes clinical events can occur suddenly, in a stable patient who is resistant to discussing prognosis, there is no value in trying to push the discussion on them.

However, if a patient is ambivalent or resistant about discussing prognosis, but is clinically declining, then the clinician will need to identify what the dilemma or obstacle is in preventing an honest discussion of prognosis [52]. By naming the dilemma and partnering with the patient, often the conversation about prognosis can move forward. An example might be, "Mr. Jones, we have been talking a lot about your children the past few weeks. I know you want to live to see your children grow and you don't want to burden them either. However, your recent CAT scan shows that your disease is getting worse despite your treatment. I think we should discuss what all of this means: for you and for your family." The key point is to identify the obstacle [52]. This shows the patient that you have been listening to them and that you understand what issues are most important to them. This will provide a layer of trust that is often necessary to have a more frank discussion [52].

4. *The fourth and final step is to deliver prognostic information tailored to patient readiness and clinical urgency* [52]. When a patient demonstrates readiness to discuss prognosis—an approach that has been published is the Ask, Tell, Ask approach [55]—this strategy begins with asking the patient what they understand and what type of information they would like ("Ask") [52]. Some patients are interested in expected survival times, while others may be more interested in future disease-related complications. The clinician then provides the information ("Tell") [52].

   Once the patient receives the information, the clinician must be prepared for the emotional response of the patient. The response to these emotions can be as simple as touching the patient softly, offering brief periods of silence for reflection, reframing hopes, or "I wish" statements [52]. "I wish" statements include statements like, "I wish I had better news today" or "I wish the CAT scan had better results, but I want you to know that we will continue to care for you." Following this, the clinician should "Ask" the patient if they understand the current situation and what has been explained [52].

   If a patient remains resistant to discussing prognosis but there is clinical urgency, again the clinician must identify the dilemma and partner with the patient [52]. Statements like, "I can tell that trying one more round of chemotherapy is very important for you, and that discussing your prognosis is painful and difficult. However, my concern is that if we don't try to speak honestly about your progress, it could prevent us from making decisions that are consistent with your values and your wishes for you and your family."

Cultivating prognostic awareness is a skill that speaks to truly patient-centered care. The National Academy of Medicine published an influential monograph, *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis*, in 2013 [56]. In this publication, the authors list 10 specific recommendations on achieving high-quality cancer care. In their first recommendation, the authors specifically recommend that patients and families receive understandable information on prognosis [56]. In their second recommendation, the authors suggest that the cancer care team should provide patients with end-of-life care consistent with their needs, values, and preferences [56]. Both of these recommendations speak to the importance of prognostic awareness. The American Society of Clinical Oncology has also published a statement that focuses on delivering individualized care to patients with advanced incurable cancer [57]. The authors of this paper recommend that patients should be well-informed of their prognosis and be given an opportunity to express their preferences and concerns [57].

During these difficult conversations, clinicians need to explore the patient's needs, values, and preferences. This information will help facilitate honest discussions of prognosis. Ultimately, it is hoped that patients and clinicians can mutually identify the level of care that matches the patient's values.

Discussing Refractory Disease with Patients

The management of the patient with metastatic gastrointestinal malignancies has become much more complicated over the past 10–15 years. Specifically, the median survival in metastatic colorectal cancer has improved from 10–12 months to greater than 30 months. This survival time is punctuated by a series of chemotherapy and biological therapies. However, as the patient nears the end stage of their disease, further antineoplastic therapy is no longer beneficial and can contribute to a decrease in a patient's quality of life. Some patients, however, find it very difficult to accept an end to attempts at chemotherapy, and some of these patients report that they are hoping for a miracle. The question that arises is how best to negotiate these clinical scenarios.

There are little empirical data to help guide these discussions. Widera and colleagues have written an excellent review of this topic, utilizing a literature review as a guide to this question. Initially, they cite a survey of 35,000 Americans, which noted that 79% of respondents believed in miracles. In another survey of the general public and trauma professionals, 61% of the public felt that a miracle could save a patient in a persistent vegetative state compared to just 20% of trauma professionals. Additionally, 57% believed that divine intervention could save a person when the physician felt that futility had been reached [58].

Knowing that the belief in miracles is relatively common, the next question that Widera outlined was to delineate what patients and surrogates mean when they are hoping for a miracle. There have been conflicting answers to that question. Some believe that this hope is "grounded in the belief in divine supernatural intervention that supercedes the laws of nature." Others believe that the hope for a miracle is simply an expression of hope or optimism. Finally, this hope for a miracle could also be a manifestation of denial of the serious illness or an expression of anger and frustration [58].

Another question that arises is whether a belief in miracles influences the medical care that is delivered. In one study of 68 patients with advanced stage lung or colon cancer, patients were asked to what extent divine intervention might change the course of their illness. The authors observed that a belief in miracles or divine intervention was associated with a preference for cardiopulmonary resuscitation. Other studies have investigated whether a physician's belief that

medical care was futile influenced a surrogate's decision regarding the futility of interventions. These studies demonstrated that a significant percentage of surrogates doubted a physician's ability to predict futility. The surrogates that doubted the physician's prediction abilities were more likely to request continuation of life support measures. Another observation from these studies is that only 2% of surrogates base their view of the patient's prognosis ***solely*** on the physician's prognostic estimate. Surrogates weigh other issues including the patient's will to live, their own observation of the patient, the power of their own support and presence, and optimism, intuition, and faith [58].

Finally, the question that arises is how might clinicians help patients and surrogates to navigate these very complex decisions. There are 2 important studies that provide some insight. Balboni and colleagues studied 343 outpatients with incurable cancer and followed them until their deaths. They studied their caregivers as well. One important observation from the study was that patients with high religious coping characteristics (patients previously shown to request aggressive care at the end of life) were more likely to receive hospice care and less likely to receive aggressive care near the end of life if the patients felt like the medical team had provided spiritual support [59].

Secondly, Lautrette and colleagues performed a randomized trial of standard care versus a communication strategy utilizing a standardized communication process (the VALUE strategy) and providing a detailed brochure on death and dying to families of gravely ill patients in the intensive care unit [60]. The VALUE strategy concentrates on the following:

1. *V*aluing what surrogates are communicating
2. *A*cknowledging their emotions
3. *L*istening carefully
4. *U*nderstanding who the patient is
5. *E*liciting questions

The researchers found that at 90 days post death, the surrogates in the intervention group had fewer symptoms of anxiety and depression as well as less posttraumatic stress [60].

So when patients and surrogates communicate that they believe in miracles, the clinician should consider the following:

1. Belief in miracles is very common.
2. Belief in miracles can influence medical care such as aggressive care at the end of life.
3. The physician's prediction of prognosis is only one of the many aspects that families and surrogates use to make decisions.
4. Providing spiritual support can help decrease overly aggressive end-of-life care.
5. When holding family meetings, concentrating on listening to family members, acknowledging their emotions and points of view, trying to understand the patient and getting to know him/her, and eliciting questions can influence the experience of the surrogate and family.

When to Discuss Early Palliative Care

Palliative care as a separate medical specialty is a rapidly growing field of medicine. Palliative care has been variably defined but generally is focused on improving a patient's quality of life by managing pain and other distressing symptoms of a serious illness. Palliative care can be provided along with other medical treatments and is not reserved for end-of-life care. As the practice of medical oncology has grown increasingly complex, there has been an equal increase in the components of care that compete for the time of the oncology clinician. In patients with metastatic and incurable disease, there often is not adequate time to comprehensively address symptoms, spiritual, social, and emotional aspects of the disease, and a thorough discussion of prognosis and how to shape the final chapter of the patient's life. The palliative care practitioner is often called in to address these aspects of the patient's illness.

The timing of palliative care, however, remains controversial. There are certainly those that equate palliative care with hospice care, and thus, the palliative care professional is not asked to see the patient until they are very near the end of their life. In a patient with newly diagnosed metastatic cancer, it may not be clear what the "pace" of the disease will be and palliative care involvement is deferred until more information on the natural history of the disease is available. However, there are now 3 randomized trials that try to address the timing of palliative care in advanced cancer.

The first study was reported by Temel and colleagues. They randomized 151 patients with advanced incurable non-small cell lung cancer to immediate palliative care consultation at diagnosis versus routine care. The study was small, and only 107 patients completed both initial and 12-week assessments. However, the study was able to demonstrate less depressive symptoms in the intervention group and improvement in quality of life. There also was less aggressive care at the end of life in the intervention group. In a secondary analysis, the palliative group had an improvement in median survival (11.6 months vs. 8.9 months) [61]. Despite methodological shortcomings, this study has been widely cited as evidence for the value of early palliative care in advanced non-small cell lung cancer.

In a second study, Zimmerman and colleagues randomized 461 patients with a variety of incurable malignancies to early palliative care versus standard care. Their intervention included a comprehensive consultation followed by tele-

phone contact as needed and monthly clinic visits. This study utilized a number of quality-of-life instruments. At 4 months, 4 of 5 quality-of-life measures favored early palliative care. Overall survival was not reported [62].

Finally, Bakitas and colleagues reported their randomized trial of early versus delayed palliative care in advanced incurable cancer. They randomized 207 patients to either immediate palliative care, which consisted of a palliative care consultation, 6 weekly telephone coaching session by a nurse, and monthly follow-up, or the same intervention initiated 3 months after diagnosis. In their study, they did not identify an improvement in quality-of-life measures with early versus delayed palliative care. However, 1-year survival favored the early intervention group (63% vs. 48%), and median overall survival also favored the early palliative care group [63].

What these 3 studies tell us is that early palliative care is a safe intervention. Early palliative care does not appear to damage quality of life, and early palliative care does not appear to decrease overall survival. The timing of palliative care interventions will depend on the availability of palliative care expertise in your community and their capacity. It will also be dependent on how open the oncology clinician and the patient/family are to early palliative care involvement. It is worth pointing out that the number of palliative care practitioners in the US is not nearly enough to care for each advanced cancer patient. Thus, ASCO and the American Academy of Hospice and Palliative Medicine have published a guidance statement outlining the palliative care skills that all oncology practitioners should possess [64]. It is hoped that there will be enhanced training for oncology fellows in the coming years so that these goals can be realized.

Recommendations on Communication During Transitions in the Care of the Patient

The National Academy of Medicine, as noted, has published a monograph that provides a road map for enhancing the care of the cancer patient. An overarching theme of this monograph is that oncology care should be patient-centered, and focused on the needs, values, and preferences of the patient. They recommend that patients and families be provided understandable information about cancer prognosis, treatment benefit and harms, palliative care, psychosocial support, and costs [56]. This task is daunting, and often these conversations are emotionally charged and challenging on many fronts. It is also noteworthy that most oncologists have not been trained in executing these conversations. In this section, a protocol published by Dizon and Back will provide guidance on how to achieve shared decision-making in the setting of transitions in care [65].

Shared decision-making "involves discussing options and their potential outcomes, eliciting patient preferences, acknowledging the decision and any associated uncertainty, and agreeing on a plan to reevaluate the decision." [65]. During transitions in a patient's course, working toward shared decision-making requires a concerted effort by the clinician to elicit patient preferences in the context of an evolving clinical situation:

1. *A first step during these meetings is to set the tone to invite participation*. This includes making sure you are in a private and quiet place, that the patient is fully dressed and comfortable, that supportive family are with him/her, and that you gain permission from the patient to discuss the issues at hand.
2. *A second step is to ensure that all parties have an understanding of the past*. This might include reviewing the past treatment history briefly so that you can transition to the current problem and the next steps. This step can often improve rapport with patients and families [65].
3. *A third step is to outline treatment options*. This step is often fraught with language that can create emotional reactions. Words like "there is nothing more we can do" or "you have failed second-line chemotherapy" can create emotions such as abandonment or blame, respectively. Using plain language that outlines the risks and potential benefits of each option will allow the patient and family to sort out what fits best with their own goals and preferences. If the clinician feels that palliative care is the best option, the patient will still want to know how palliative care would be consistent with his/her needs, values, and preferences [65].
4. *A fourth step is to step back and notice and observe the patient for an emotional reaction*. This may require a period of silence. The clinician should try to name the emotion and when it is appropriate, an empathic statement will help comfort the patient. Statements like: "I can tell that today's news is very difficult." Or, "I can see that you are angry about today's results. It is normal to be angry and frustrated." Or, " I wish the CAT scan had a better result." The goal of this step is for the patient to feel that the physician understands what they are going through [65].
5. *A fifth step is to acknowledge uncertainty* [65]. With every transition in care, there is uncertainty. "Will the next line of chemotherapy be effective? Will palliative care keep my pain under control? What are the odds of getting back into remission?" The clinician needs to honestly acknowledge this uncertainty, being careful not to provide unrealistic expectations. Again, there is language here that can lead to misunderstanding. If a treatment option is never associated with complete remissions, it is unfair to the patient to use a phrase such as, "We need to get treatment

started so that we can get the cancer back into remission." A more honest phrase might be, "In this situation, we are now using a third type of chemotherapy. What we know about this treatment is that about 30% of the time, the cancer will either stay stable or even shrink 25–50%. This treatment will not cure your disease or put it back into remission, but we hope it will help preserve your quality of life."

6. *A sixth step is to titrate information* [65]. The clinician needs to provide information that will be helpful and useful for the patient to make a decision. Sometimes providing extraneous information will distract the patient from the core issue. If a patient has stage III colon cancer and your recommendation is for chemotherapy, it may not be helpful to mention the nuclear grade of the tumor. The nuclear grade will not alter your recommendation and may not be a reproducible risk factor for recurrence. Titrating information will also be helpful if you believe that other issues should wait for another session, such as saying, "That is a very good question. The answer is somewhat complicated. I am not trying to avoid the issue, but I would prefer to discuss your question next week when your husband will be able to join us."
7. *A seventh step is to clarify what role the patient wants to take in the decision-making* [65]. This step can be accomplished at any time and often would have been clarified at a prior meeting. Shared decision-making does not always mean that the patient makes his/her own decision after getting all the facts. Sometimes the options are overwhelming the patient, and they simply want the clinician to make a strong recommendation. One might say, "So today we have talked about a lot of options. Would you like my recommendation or would you like to discuss this with your family and get back to me tomorrow?"
8. *An eighth step is to incorporate the patient's concerns into your recommendation and discussion*. This requires us to ask what is worrying the patient the most [65]. If the patient previously had a life-threatening neutropenic sepsis episode, she may be most worried about taking another drug that is likely to cause neutropenia again. Or the patient may use her hands for a hobby or vocation and wants to avoid neuropathy. The key part of this step is to ask the patient their biggest concern. It can be useful to say something like, "After hearing the options and the pros and cons of each, what worries you the most about the next step?"
9. *A ninth step when discussing transitions is communicating prognosis* [65]. It is useful to specifically ask if the patient desires to know about prognosis and the expectations from this treatment. For example: "Some people want to know what the future may bring. Would you like to talk about prognosis and the future today?" Patients are also very different in how they want prognostic information communicated. So it helps to ask, "Some people want very black-and-white numbers and percentages, while others just want a general idea of our expectations. How would you like me to talk about this?"

Communication during transitions is a very important part of practicing GI oncology. In chronic diseases such as metastatic colon cancer, there may be as many as 5–10 transitions of care over the life of the patient. Managing these transitions and involving patients and families with the decisions can provide the patient a much more favorable quality of life over the span of their illness. Being prepared for these transitions, being sure the patient is supported with family during transitions, and responding to emotions can strengthen the clinician–patient bond, and help make future transitions easier to navigate.

Conclusion

The care of the patient with GI malignancies can be a very rewarding experience. With more effective therapies available, a patient's quality of life can be maintained and their survival times can be extended. The clinician caring for these patients must not only be skilled at administering chemotherapy, but must also gain skills in pain and symptom management, assessment of other syndromes such as depression, and must become prepared to participate in emotionally charged meetings with their patients. It is hoped that this chapter laid the groundwork for the GI oncology clinician to begin to gain these skills.

References

1. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Besh S, Chao J, National Comprehensive Cancer Network, et al. Esophageal and esophagogastric junction cancer, version 1.2015. J Natl Compr Cancer Netw. 2015;13(2):194–227.
2. Dai Y, Li C, Xie Y, Liu X, Zhang J, Zhou J, Pan X, Yang S. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev. 2014;10:CD005048.
3. Homs MY, Steyerberg EW, Eijkenboom WM, Tilanus HW, Stalpers LJ, Bartelsman JF, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet. 2004;364(9444):1497–504.
4. Adamson D, Blazeby J, Nelson A, Hurt C, Nixon L, Fitzgibbon J, et al. Palliative radiotherapy in addition to self-expanding metal stent for improving dysphagia and survival in advanced oesophageal cancer (ROCS: Radiotherapy after Oesophageal Cancer Stenting): study protocol for a randomized controlled trial. Trials. 2014;15:402.
5. Yang K, Liu K, Zhang WH, Lu ZH, Chen XZ, Chen XL, et al. The value of palliative gastrectomy for gastric cancer patients with intraoperatively proven peritoneal seeding. Medicine (Baltimore). 2015;94(27):e1051.

6. Sun J, Song Y, Wang Z, Chen X, Gao P, Xu Y, et al. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis. BMC Cancer. 2013;13:577.
7. Fujitani K, Yang HK, Kurokawa Y, Park DJ, Tsujinaka T, Park BJ, Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group, Korea Gastric Cancer Association, et al. Randomized controlled trial comparing gastrectomy plus chemotherapy with chemotherapy alone in advanced gastric cancer with a single non-curable factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01. Jpn J Clin Oncol. 2008;38(7):504–6.
8. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: gastric cancer version 3.2015. NCCN. http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
9. Paul Olson TJ, Pinkerton C, Brasel KJ, Schwarze ML. Palliative surgery for malignant bowel obstruction from carcinomatosis: a systematic review. JAMA Surg. 2014;149(4):383–92.
10. Kucukmetin A, Naik R, Galaal K, Bryant A, Dickinson HO. Pallliative surgery versus medical management for bowel obstruction in ovarian cancer. Cochrane Database Syst Rev. 2010;7:CD007792.
11. Henry JC, Pouly S, Sullivan R, Sharif S, Klemanski D, Abdel-Misih S, et al. A scoring system for the prognosis and treatment of malignant bowel obstruction. Surgery. 2012;152(4):747–56; discussion 756–7.
12. Laval G, Marcelin-Benazech B, Guirimand F, Chauvenet L, Copel L, Durand A, French Society for Palliative Care, French Society for Digestive Surgery, French Society for Gastroenterology, French Association for Supportive Care in Oncology, French Society for Digestive Cancer, et al. Recommendations for bowel obstruction with peritoneal carcinomatosis. J Pain Symptom Manag. 2014;48(1):75–91.
13. Peng X, Wang P, Li S, Zhang G, Hu S. Randomized clinical trial comparing octreotide and scopolamine butylbromide in symptom control of patients with inoperable bowel obstruction due to advanced ovarian cancer. World J Surg Oncol. 2015;13:50.
14. Currow DC, Quinn S, Agar M, Fazekas B, Hardy J, McCaffrey N, et al. Double-blind, placebo-controlled randomized trial of octreotide in malignant bowel obstruction. J Pain Symptom Manag. 2015;49(5):814–21.
15. Feuer DJ, Broadley KE. Corticosteroids for the resolution of malignant bowel obstruction in advanced gynecological and gastrointestinal cancer. Cochrane Database Syst Rev. 2000;2:CD001219.
16. Clark K, Lam L, Currow D. Reducing gastric secretions–a role for histamine 2 antagonists or proton pump inhibitors in malignant bowel obstruction? Support Care Cancer. 2009;17(12):1463–8.
17. Kawata N, Kakushima N, Tanaka M, Sawai H, Imai K, Hagiwara T, et al. Percutaneous endoscopic gastrostomy for decompression of malignant bowel obstruction. Dig Endosc. 2014;26(2):208–13.
18. Shaw C, Bassett RL, Fox PS, Schmeler KM, Overman MJ, Wallace MJ, et al. Palliative venting gastostomy in patients with malignant bowel obstruction and ascites. Ann Surg Oncol. 2013;20(2):497–505.
19. Lavu H, Lengel HB, Sell NM, Baiocco JA, Kennedy EP, Yeo TP, et al. A prospective, randomized, double-blind, placebo controlled trial on the efficacy of ethanol celiac plexus neurolysis in patients with operable pancreatic and periampullary adenocarcinoma. J Am Coll Surg. 2015;220(4):497–508.
20. Lillemoe KD, Cameron JL, Kaufman HS, Yeo CJ, Pitt HA, Sauter PK. Chemical splanchnicectomy in patients with unresectable pancreatic cancer: a prospective randomized trial. Ann Surg. 1993;217(5):447–55; discussion 456–7.
21. Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. Cochrane Database Syst Rev. 2011;3:CD007519.
22. Portenoy RK, Ahmed E. Principles of opioid use in cancer pain. J Clin Oncol. 2014;32(16):1662–70.
23. Hui D, Bruera E. A personalized approach to assessing and managing pain in patients with cancer. J Clin Oncol. 2014;32(16):1640–6.
24. Smith TJ, Saiki CB. Cancer pain management. Mayo Clin Proc. 2015;90(10):1428–39.
25. Brecher DB, West TL. Pain management in a patient with renal and hepatic dysfunction. J Palliat Med. 2014;17(2):249–52.
26. Smith HS. Opioid metabolism. Mayo Clin Proc. 2009;84(7):613–24.
27. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, Implantable Drug Delivery Systems Study Group, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity and survival. J Clin Oncol. 2002;20(19):4040–9.
28. Smith TJ, Coyne PJ, Staats PS, Deer T, Stearns LJ, Rauck RL, et al. An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug-related toxicity, and possibly better survival compared with comprehensive medical management (CMM). Ann Oncol. 2005;16(5):825–33.
29. Gulati A, Puttanniah V, Hung J, Malhotra V. Considerations for evaluating the use of intrathecal drug delivery in the oncologic patient. Curr Pain Headache Rep. 2014;18(2):391.
30. Deer TR, Smith HS, Burton AW, Pope JE, Doleys DM, Levy RM, Center for Pain Relief, Inc., et al. Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. Pain Physician. 2011;14(3):E283–312.
31. Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): what we need and what we know. J Peripher Nerv Syst. 2014;19(2):66–76.
32. Avan A, Postma TJ, Ceresa C, Avan A, Cavaletti G, Giovannetti E, et al. Platinum-induced neurotoxicity and preventive strategies: past, present, and future. Oncologist. 2015;20(4):411–32.
33. Pachman DR, Qin R, Seisler DK, Smith EM, Beutler AS, Ta LE, et al. Clinical course of oxaliplatin-induced neuropathy: results from the randomized phase III Trial N08CB (Alliance). J Clin Oncol. 2015;33(30):3416–22.
34. Albers JW, Chaudhry V, Cavaletti G, Donehower RC. Interventions for preventing neuropathy caused by cisplatin and related compounds. Cochrane Database Syst Rev. 2014;3:CD005228.
35. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, American Society of Clinical Oncology, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32(18):1941–67.
36. Loprinzi CL, Qin R, Dakhil SR, Fehrenbacher L, Flynn KA, Atherton P, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). J Clin Oncol. 2014;32(10):997–1005.
37. Gamelin L, Boisdron-Celle M, Delva R, Guérin-Meyer V, Ifrah N, Morel A, et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res. 2004;10(12 Pt 1):4055–61.
38. Grothey A, Nikcevich DA, Sloan JA, Kugler JW, Silberstein PT, Dentchev T, et al. Intravenous calcium and magnesium for oxaliplatikn-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. J Clin Oncol. 2011;29(4):421–7.
39. Swami U, Goel S, Mani S. Therapeutic targeting of CPT-11 induced diarrhea: a case for prophylaxis. Curr Drug Targets. 2013;14(7):777–97.
40. Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD. Can UGT1A1 genotyping reduce morbidity and mortality in patients

with metastatic colorectal cancer treated with irinotecan? An evidence-based review. Genet Med. 2009;11(1):21–34.
41. Shulman K, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowicz F, et al. Clinical implications of UGT1A1∗28 genotype testing in colorectal cancer patients. Cancer. 2011;117(14):3156–62.
42. Deeken JF, Slack R, Marshall JL. Irinotecan and uridine diphosphate glucuronosyltransferase 1A1 pharmacogenetics: to test or not to test, that is the question. Cancer. 2008;113(7):1502–10.
43. Benson AB 3rd, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA Jr, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22(14):2918–26.
44. Labori KJ, Hjermstad MJ, Wester T, Buanes T, Loge JH. Symptom profiles and palliative care in advanced pancreatic cancer: a prospective study. Support Care Cancer. 2006;14(11):1126–33.
45. Sebti J, Desseigne F, Saltel P. Prodromal depression in pancreatic cancer: retrospective evalution on ten patients. Palliat Support Care. 2015;13(3):801–7.
46. Breitbart W, Rosenfeld B, Tobias K, Pessin H, Ku GY, Yuan J, et al. Depression, cytokines, and pancreatic cancer. Psychooncology. 2014;23(3):339–45.
47. Andersen BL, DeRubeis RJ, Berman BS, Gruman J, Champion VL, Massie MJ, American Society of Clinical Oncology, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol. 2014;32(15):1605–19.
48. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.
49. Boyd CA, Benarroch-Gampel J, Sheffield KM, Han Y, Kuo YF, Riall TS. The effect of depression on stage at diagnosis, treatment, and survival in pancreatic adenocarcinoma. Surgery. 2012;152(3):403–13.
50. Prasad SM, Eggener SE, Lipsitz SR, Irwin MR, Ganz PA, Hu JC. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate cancer. J Clin Oncol. 2014;32(23):2471–8.
51. Weeks JC, Catalano PJ, Cronin A, Finkelman MD, Mack JW, Keating NL, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367(17):1616–25.
52. Jackson VA, Jacobsen J, Greer JA, Pirl WF, Temel JS, Back AL. The cultivation of prognostic awareness through the provision of early palliative care in the ambulatory setting: a communication guide. J Palliat Med. 2013;16(8):894–900.
53. Temel JS, Greer JA, Admane S, Gallagher ER, Jackson VA, Lynch TJ, et al. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care. J Clin Oncol. 2011;29(17):2319–26.
54. Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA. 2008;300(14):1665–73.
55. Back AL, Arnold RM, Baile WF, Tulsky JA, Fryer-Edwards K. Approaching difficult communication tasks in oncology. CA Cancer J Clin. 2005;55(3):164–77.
56. Levit LA, Balogh EP, Nass SJ, Ganz PA, editors. Delivering high quality cancer care: charting a new course for a system in crisis. Washington, DC: The National Academies Press; 2013.
57. Peppercorn JM, Smith TJ, Helft PR, Debono DJ, Berry SR, Wollins DS, American Society of Clinical Oncology, et al. American Society of Clinical Oncology statement: toward individualized care for patients with advanced cancer. J Clin Oncol. 2011;29(6):755–60.
58. Widera EW, Rosenfeld KE, Fromme EK, Sulmasy DP, Arnold RM. Approaching patients and family members who hope for a miracle. J Pain Symptom Manag. 2011;42(1):119–25.
59. Balboni TA, Paulk ME, Balboni MJ, Phelps AC, Loggers ET, Wright AA, et al. Provision of spiritual care to patients with advanced cancer: associations with medical care and quality of life near death. J Clin Oncol. 2010;28(3):445–52.
60. Lautrette A, Darmon M, Megarbane B, Joly LM, Chevret S, Adrie C, et al. A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med. 2007;356(5):469–78.
61. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363(8):733–42.
62. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet. 2014;383(9930):1721–30.
63. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol. 2015;33(13):1438–45.
64. Bickel KE, McNiff KK, Buss MK, Kamal A, Lupu D, Abernethy AP, et al. Defining high-quality palliative care in oncology practice: an ASCO/AAHPM guidance statement. J Clin Oncol. 2015;33(29 suppl):108.
65. Dizon DS, Politi MC, Back AL. The power of words: discussing decision making and prognosis. Am Soc Clin Oncol Educ Book. 2013:442–6.

Gastrointestinal Cancers and Thrombosis

21

Arnab Basu and Alok A. Khorana

Introduction

Thromboembolism is an important cause of mortality and morbidity in patients with cancer. This complication comprises venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), and arterial events such as stroke and myocardial infarction. Armand Trousseau is the physician most linked with the clinical syndrome of hypercoagulability in cancer based on his lectures from 1865, although it is likely the association was noticed first by Jean Baptiste Bouillaud in 1823 [1]. Thromboembolism is widely prevalent across a variety of cancers but is especially noted among patients with gastrointestinal cancers, a heterogeneous group including esophageal, gastric, pancreatic, hepatobiliary, colorectal, and anal cancers. VTE is often the initial manifestation of cancer, with an incidence of about 1–2% in unselected cancer patients [2]. In patients with gastrointestinal cancers, incidence rates are higher, with studies estimating risks to be 7- to 20-fold compared to the general population [3–5]. Progress has been made in identifying some key determinants and mechanisms of this phenomenon, and several studies are being conducted aimed at identifying patients at high risk who may benefit from prophylactic anticoagulation. We present an overview of the evidence related to epidemiology, mechanisms, prevention, and treatment of VTE in gastrointestinal cancers.

A. Basu
Department of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA

A. A. Khorana (✉)
Gastrointestinal Malignancies Program, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: Khorana@ccf.org

Epidemiology

Due to the substantial variation in the presentation of VTE across the various subtypes of cancers, we review the epidemiology separately by type of cancer. Unfortunately, there are challenges to interpreting the reported "rates" of thrombosis across various studies. These challenges arise from differing historical timeframes during data collection, different methods of quantifying risk (risk per 1000 person years versus lifetime cumulative risk versus annualized or short-term incidence), and various settings (inpatient versus outpatient, single-center versus population-based record linkage studies). Nevertheless, these studies provide valuable insight into the considerable expected risk of VTE in gastrointestinal cancers.

Esophageal Cancer

There were an estimated 16,980 new cases of esophageal cancer in the United States in 2015 and an estimated 15,590 deaths [6]. Thrombosis in esophageal cancer also contributes to mortality. In a Dutch record linkage study by Blom et al., the incidence rate for VTE in esophageal cancer was estimated at 12.5 (95% confidence interval [CI], 7.3–21.4) events per 1000 patients in the first 6 months after diagnosis [2]. Similarly, a study examining data from hospitalized patients with cancer using the National Hospital Discharge Survey found an incidence of 20 diagnoses of VTE per 1000 hospitalizations for esophageal cancer [7]. An analysis of the Danish cohort by Cronin-Fenton et al. showed an elevated risk of hospitalization for VTE due to esophageal cancer with an adjusted incidence rate of 11.6 (95% CI, 3.8–35.0) events per 1000 person years. Esophageal, gastric, and gastroesophageal junctional tumors are all associated with significantly higher rates of VTE. In a comparative study of several chemotherapy regimens, some using cisplatin, there was an overall VTE rate of 9.4% across treatment types. Cisplatin-based therapy was associated with a doubling of thrombotic risk [8].

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_21

Gastric Cancer

The incidence of gastric cancer is falling in the Western hemisphere, with an estimated 24,590 new cases in 2015 and 10,720 estimated deaths in the United States, but it remains an important cause of cancer-related morbidity and mortality worldwide [6]. An older population-based analysis of hospital discharge data in the 1990s approximated an incidence of VTE of 85 per 10,000 patients for patients with gastric cancer versus 110 per 10,000 patients with pancreatic cancer [9]. A more recent analysis based on Surveillance, Epidemiology, and End Results (SEER) data reported a 3-month incidence of 205 per 1000 person years in these patients [10]. In a retrospective analysis based on a cohort of 3095 Korean patients with advanced gastric cancer, estimated VTE rates were 18.8 per 1000 person years, approximately 5-fold elevated compared to the general population but significantly less than seen in pancreatic cancer. In this retrospective analysis, there was a correlation between female gender, upper stomach involvement, and higher CA 19-9 levels with the development of thrombotic events [11]. There are some recently reported prospective data on VTE incidence in gastric cancer among patients receiving chemotherapy, which found an incidence of 40.1 (95% CI, 96–199) events per 1000 person years, with 56% being DVT and 12% PE events. Of note, all of these patients were on chemotherapy—a known additional risk factor for thrombosis [12].

Pancreatic Cancer

Pancreatic cancer is a relatively common and lethal diagnosis, with an estimated 48,960 new cases and 40,560 deaths occurring in 2015 in the United States [6]. Rates of VTE in pancreatic cancer are among the highest across all types of malignancies. A large European record linkage study by Blom et al. in a cohort of 66,000 patients found a cumulative incidence of 22.7 events (95% CI, 16.6–31.0) per 1000 patients, which is at the lower end of the reported spectrum but still nearly tenfold elevated over the general population [2]. Another cohort study using linked UK databases found a much higher absolute rate of 98 per 1000 patient years—the highest among all cancers in the cohort [13]. Among the highest estimates of VTE risk in pancreatic cancer included a retrospective cohort study conducted at a university hospital in the United States where about 35% of patients with pancreatic cancer presenting to the hospital and undergoing imaging had at least 1 incidental or clinically evident thromboembolic episode; 14% continued to have recurrent events [14]. A majority of these venous thrombi were located in the portal, splenic, and the superior mesenteric venous systems, although lower extremity deep veins were also often involved.

Limited prospective data seem to validate the risks estimated via these large retrospective cohort studies. A prospective study by Blom et al. followed 202 patients with pancreatic cancer and found an incidence of venous thrombosis at 108.3 per 1000 person years—a risk approximately 59 times greater than the general population [15]. Anatomic location of the tumor was related to thrombotic risk, with tumors of the pancreatic body and tail doubling the rate of VTE. Patients receiving chemotherapy for pancreatic cancer were about 4.8 times as likely to develop thrombosis [15]. Advanced stages of disease are also associated with higher rates of thromboembolism. Several studies have shown that these thromboembolic events also relate to poorer survival in patients with pancreatic cancer [14].

Hepatobiliary Cancer

Hepatocellular carcinoma (HCC) is also relatively common, with 35,660 new cases estimated in 2015 and 24,550 deaths in the United States. It is also a global problem and the third most common cancer in the developing world. Thrombosis is a major issue in liver cancer, mostly due to the involvement of the portal vein. Estimates for the incidence of portal vein thrombosis (PVT) in HCC vary from 10% to 30% [16, 17], and studies have found a high rate of PVT on autopsy [18]. Patients with cirrhosis and HCC have a very high risk of PVT (odds ratio [OR] 17.1 [95% CI, 11.1–26.4]), and other risk factors include tumor invasion of the portal vein or surgery [19, 20]. Similarly, a single-center retrospective study of 194 patients diagnosed with HCC at a tertiary referral center found factors such as the Child-Pugh score, stage of disease, involvement of major vessels, and serum markers of disease severity such as low albumin and high alpha-fetoprotein (AFP) to be significantly associated with an increased risk of PVT. Interestingly, a higher international normalized ratio (INR) was also associated with increased thrombotic risk, which emphasizes the difficulty of managing coagulopathies in liver disease. In this study, 31% of HCC patients had a PVT. Those with PVT also had a concomitant higher risk of systemic VTE events (11.5% vs 4.4%; $p = 0.04$) [21].

There are limited data on the risk of thrombosis in cholangiocarcinoma: one retrospective report based on 273 patients found a lifetime incidence of 14.6% during and after diagnosis; of these, 55% were portal and hepatic vein thrombi, while only 35% were DVT- or PE-related events [22]. A prospective cohort study examined 121 patients with cholangiocarcinoma with VTE screening on presentation and found that at cancer diagnosis 15 patients had experienced a VTE (12.4%, 95% CI, 7.1–19.6%), suggesting that VTE may be a relatively common problem in these cancers as well [23].

Colorectal Cancer

Colorectal cancer is the most common gastrointestinal malignancy. There were 132,700 estimated new diagnoses in

2015 with 49,700 expected deaths in the United States [6]. A Dutch population-based case control study (the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis [MEGA] cohort) estimated a relative risk of 16.4 (95% CI, 4.2–63.7) for a VTE event in patients with colorectal cancer when compared with the general population [5]. A large retrospective analysis of 68,000 patients with colorectal cancer demonstrated an incidence of approximately 3% over a time period of 2 years [24]. This risk of thrombosis appears greatest in the initial 6 months after diagnosis, where incidence was 50 per 1000 patient years. A meta-analysis estimated an overall incidence of 33 (95% CI, 21–53) VTE events per 1000 patient years in these patients, based on several published studies [25]. A higher stage of disease increases the risk of VTE, as does presence of metastatic disease [24]. Patients with metastatic colorectal cancer undergoing chemotherapy, a known risk factor, demonstrated rates of VTE up to 16% [26]. A large population-based case control study of patients undergoing chemotherapy studied 4548 patients with colorectal cancer. Of these, 10.6% had VTE event, in comparison to 1.4% among age-, sex-, and comorbidity-matched controls [27]. These risk factors have been corroborated in multiple studies. In a large UK cohort of 10,309 patients with colorectal cancer, the Duke stage (hazard ratio [HR] 3.08, 95% CI, 1.95–4.84), administration of chemotherapy (HR 1.39, 95% CI 1.14–1.69), and hospitalization were all associated with increasing VTE risk [28].

Colorectal surgery is known to be independently associated with an increased risk of VTE. Some studies have shown a 20–40% postoperative incidence of DVT [29, 30]. Even in the presence of VTE prophylaxis, there is a 10% postoperative risk for VTEs in patients who undergo colorectal surgery [31].

The previous UK-based cohort found an almost 3-fold greater risk for VTEs postoperatively in patients with higher Duke stages (B and C) compared to Duke Stage A disease. The risk of VTE in higher Duke stages also remained elevated postoperatively for longer than 4 weeks, while most VTE events in Duke stage A happened within the first month [28].

Anal Cancer

Anal cancers are relatively rare, afflicting an estimated 7720 new US patients in 2015 and causing 1010 estimated deaths [6]. Limited data is available on the risk of VTE in these patients. A cohort study utilizing the National Hospital Discharge Survey found an incidence of 2.1 events per 100 inpatient admissions among patients with anal carcinoma, an elevated risk, and about half the risk of pancreatic cancer at 4.3 diagnoses per 100 admissions [7]. Almost a third of these VTE events were PE. An analysis based on the Dutch cancer study found a short-term cumulative incidence of 8.9 VTE events (95% CI, 5.6–14.1) per 1000 patients within 6 months of diagnosis of anal cancer. Metastatic disease was associated with increased risk, with these patients having 12.4 events (95% CI, 4.0–37.6) per 1000 patients on average [2]. Prospective evaluation of VTE incidence in this setting is necessary to better quantify risk of VTE in anal cancer in the contemporary era.

Mechanisms of Cancer-Related Thrombosis

The high risk of thromboembolic events in gastrointestinal cancers can be explained by several factors, including tumor biology and the close anatomical supposition of these organs with major vascular systems (Fig. 21.1). In addition, all cancers, including gastrointestinal cancers, share risk factors such as increased circulating prothrombotic factors, increased

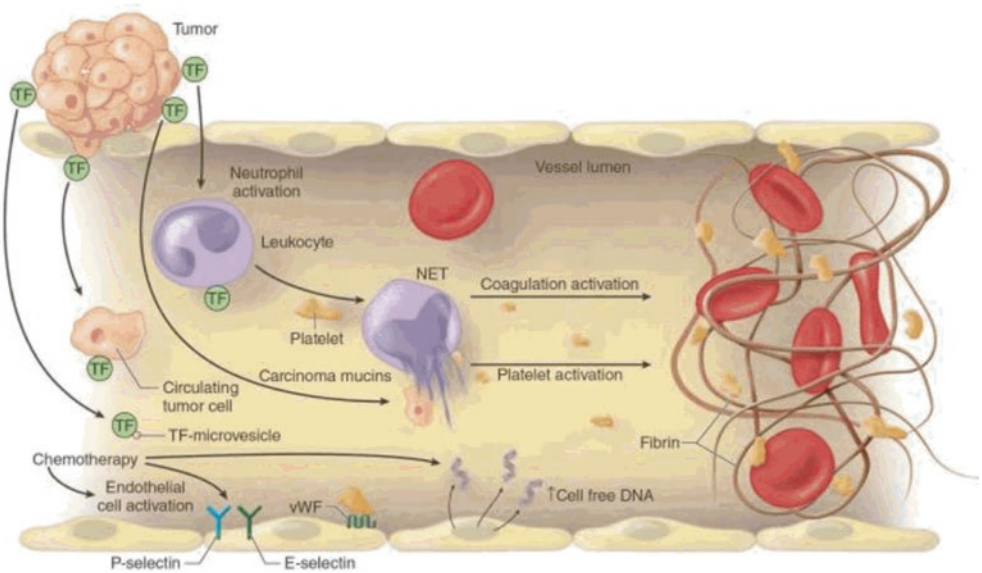


Fig. 21.1 Prothrombotic pathways in cancer. (Reproduced with permission from Lee and Khorana [77])

platelet activation, and a pro-inflammatory environment. Chemotherapy is also an additional risk factor for some of these tumors since it frequently includes antiangiogenic and/or platinum-based treatments that are known to be vasculotoxic.

Given the numerous factors associated with this phenomenon, there is a need for a theoretical framework to understand mechanisms of thrombosis. One of the most elegant and often used models for thrombosis has been the Virchow's triad, which brings together 3 broad determinants of thrombogenicity: a stasis of blood flow, endothelial injury, and hypercoagulability. While tumors of the gastrointestinal tract can frequently cause stasis as well as direct endothelial injury through extension, no factor is as important as hypercoagulability.

Procoagulant Factors

Perhaps the most studied factor leading to VTE in cancer patients is the increased expression of tissue factor (TF). TF is a glycoprotein, which in its full-length form is contained within the subendothelial vascular tissue mostly free from contact with blood and other blood components. Physiologically, when there is damage to the endothelium, TF is exposed to the vasculature. TF is a ligand for factor VII, and the TF-VIIa complex in turn activates factor X to Xa, and subsequently prothrombin to thrombin, leading to clot formation. The formation of thrombin also is a strong stimulant of the recruitment of platelets, which together lead to a stable mechanical plug.

Apart from the direct activation of the extrinsic pathway, TF also has multiple other functions, such as angiogenesis and cell signaling. TF can stimulate tumor growth and also facilitate metastatic spread [32]. Several tumors express endogenous tissue factor, and this is a prominent feature of cancers that have epithelial components such as gastrointestinal cancers. A large majority (75%) of colorectal carcinomas express tissue factor, and there is positive correlation between increased expression and metastatic disease [33]. In a study of 122 resected pancreatic cancer specimens, 77% of pancreatic intraepithelial neoplasia, 91% of intraductal papillary mucinous neoplasms, and 89% of pancreatic cancers expressed TF at elevated levels [34]. TF levels also correlate with increasing microvascular density in colorectal and pancreatic cancer and with increased expression of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) [34, 35]. Certain genetic triggers may be the reason for increased expression of TF in colorectal carcinoma—these include an activation of the *KRAS* oncogene as well as loss of function of the p53 tumor suppressor gene. An activated *KRAS* causes a PI3K/akt pathway-induced stimulation of tissue factor transcription and translation, while the loss of function of p53 releases the brakes on TF transcription that it usually suppresses. This results in greater TF expression on the surface of the colorectal cancer cells [36]. A similar mechanism operates in pancreatic cancers as well. A corroborative study demonstrated increased TF expression in a majority of patients with pancreatic carcinoma, with this expression being positively correlated with VEGF expression, higher tumor grade, and higher microvascular density [37].

Recent evidence demonstrates that apart from directly expressing TF on the cell surface, cancer cells also shed TF into the circulation, via the release of TF-bearing microparticles (TF-MPs). Microparticles are one of the three major forms of cellular membrane vesicles, with a radius of 0.1–1 μ[mu]m, and other membrane vesicles include the exosomes (50–100 nM) and apoptotic bodies (1–3 μ[mu]M). These TF-MPs are found in great numbers in pancreatic carcinoma [38]. In a murine model of pancreatic cancer-induced thrombosis, infusion of TF-MPs results in a much greater incidence of VTEs versus controls [39]. Tumors are known to release exosomes rich in TF especially during epithelial-mesenchymal transition [40]. This evidence lends support to the hypothesis that TF can promote the metastatic process [41]. In addition, TF-MPs are covered with negatively charged phospholipids, and as a result, these particles easily interact with positively charged coagulation protein complexes and can aid in their assembly and trigger coagulation. The role of tumor cell-generated microparticles in thrombosis and metastasis is a focus of continued investigation.

Platelet-Related Factors

Platelets are a major component of the intravascular environment and play a key role in hemostasis. There are emerging data regarding the importance of platelets in the cancer-microenvironment interaction. Most microparticles in the bloodstream are actually derived from platelets. Indeed, microparticles in the circulation are sometimes called "platelet dust" [42]. In addition, platelets are some of the largest peripherally circulating source of cytokines, such as transforming growth factor-β(beta)1 (TGF-β1). There has been increasing interest recently in understanding the interaction of tumors with platelets. During the process of thrombogenesis under physiologic conditions, typically the release of TF and activation of the extrinsic pathway occur in the first phase, which then leads to a recruitment of platelets in the second phase to form "the platelet plug." The platelet phase makes way for the mature factors such as fibrin to form and tightly bind the clot in order to form the "fibrin plug." Tumors, by virtue of expressing TF and by releasing numerous cytokines and microparticles, cause a disruption in the microenvironment. We now understand a phenomenon of

tumor cell-induced platelet aggregation (TCIPA). Cancer cells can frequently express on their surface factors that are procoagulant, including TF, which can automatically lead to the initiation of the platelet phase of the blood clot, causing platelet activation and aggregation. There is evidence that increasing TCIPA may be associated with a higher incidence of metastatic disease and a more aggressive disease course. Apart from TF, several other pro-aggregation factors are also released by tumors. One such factor is adenosine diphosphate (ADP), a known platelet agonist. Increased ADP secretion by tumors has been observed in lung cancers, neuroblastoma, melanoma, and other tumor types [43–45]. Apart from ADP, thromboxane A_2 (TXA_2), a potent prothrombotic arachidonic acid derivative and platelet activator, is also generated as part of the interaction between platelets and cancer cells, and is highly expressed by tumor cells such as in colorectal cancer [46]. TXA_2 is also produced by activated platelets and also leads to further platelet activation and aggregation. TXA_2 increases the expression of adhesion molecules on platelet surface such as the GpIIb/IIIa. Another important platelet surface receptor, P-selectin, is a cell adhesion molecule that is expressed in activated platelets, and is known to be a possible marker for thrombotic risk [47]. There are many studies that show an increased expression of P-selectin through contact with cancer cells [48]. Also, some recent studies show that a higher rate of P-selectin deposition and aggregation with colon cancer cells was associated with a higher rate of metastasis and tumor growth [49], and also likely contributes to a higher risk of thrombosis in that subset of patients [48]. Some recent studies have shown increased platelet activation and aggregation both in higher stages of cancer as well as increasing activation based on future thrombotic risks in these patients [50].

Genetic Determinants

While we have explored briefly the increased release of primal factors such as TF, the increased expression of prothrombotic molecules by cancer cells, and also the further downstream effects in the coagulation cascade such as the platelet phase and fibrin clot formation, there are further upstream genetic triggers that underlie the prothrombotic phenotype in cancer patients. It is important to understand the molecular characteristics of the gastrointestinal tumors that lend themselves to the increased risk of thrombosis. We previously mentioned that *KRAS* mutations may drive higher levels of TF expression in cancer cells through PI3k/akt activation and plausibly increase the risk of thrombosis in cancer patients. *KRAS* mutations are also associated with an increased release of pro-inflammatory cytokines such as IL-8 and IL-6 and growth factors such as G-CSF [51, 52]. Until recently little information was available on the clinical measure of this risk. A recent retrospective cohort study examined this question in a population of 172 metastatic colorectal carcinoma patients. The risk of VTE was analyzed from 6 months prior to diagnosis to any time after diagnosis of mCRC. Incidence of VTE in patients with activated mutated *KRAS* was 32%, in comparison to 17.8% in wild-type *KRAS*. The odds ratios for this association were 2.21 (95% CI, 1.08–4.53). The association remained statistically significant when adjusted for other factors, such as the use of antiangiogenic therapy with bevacizumab, and after adjusting for validated measures of cancer thrombotic risk, modeled by the Khorana score, suggesting an underlying causative relationship otherwise not captured by either means. A logistic regression model adjusting for Khorana score, *KRAS*, and their statistical interaction increased the estimate for the odds ratio for VTE to 6.23 (95% CI, 1.56–24.96) when comparing patients with a mutation versus not [53].

Most gastrointestinal cancers are predominantly adenocarcinomas, characterized by a glandular structure and increased mucin production. Carcinoma cells upregulate production of mucin through genes such as MUC1, MUC2, MUC4, and MUC16. Mucin is known to interact with L-selectin and P-selectin. There is evidence to suggest that interactions with mucins can spontaneously cause a phenomenon resembling the Trousseau syndrome in mouse models [54].

Apart from this, there are a plethora of other described oncogenic mutations such as *HER2, EGFR*, *MET*, *PTEN*, and *TP53*, which apart from driving the cancer phenotype also may be involved in the hypoxia-angiogenesis pathway, upregulation of TF expression and release, and also increase of the expression of coagulation factors such as factors II and VII and the protease-activated receptors PAR-1 and PAR-2 [55].

Chemotherapy-Related Factors

An additional environmental factor that may enhance thrombogenesis in gastrointestinal cancers is systemic antineoplastic therapy. Chemotherapy can have a variety of side effects such as direct endothelial injury and increased tumor cell lysis causing release of prothrombotic factors. Cisplatin-based therapy has been shown to be associated with an increased level of von Willebrand factor (vWF) [56]. Starling et al. conducted an exploratory prospective analysis on the data for the Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer-2 (REAL-2) trial, which had 1002 patients with advanced esophageal/gastric or gastroesophageal (GE) junctional cancers randomized to compare between 4 different triplet chemotherapy regimens, including ECF (epirubicin/cisplatin/fluorouracil), EOX

(epirubicin, oxaliplatin, and capecitabine), EOF (epirubicin plus oxaliplatin and 5-fluorouracil), and ECX (epirubicin with cisplatin and capecitabine). Patients were followed for both arterial and venous thromboembolic events (TEs), the incidence of which was the primary endpoint. Of 964 patients, 11.4% (95% CI, 9.4–13.4%) had thromboembolic events (both arterial and venous), while 9.4% (95% CI, 7.6–11.3%) had venous thromboembolic events. In multivariate analysis, there was a lower risk of thromboembolism with oxaliplatin when compared to cisplatin (HR 0.51 [95% CI, 0.34–0.76]). Thrombotic rates were similar with the fluoropyrimidines, capecitabine versus fluorouracil (HR 0.84 [95% CI, 0.57–1.22]). ECF was the most thrombogenic regimen with 15.3% patients having thrombotic events (a large proportion CVAD-associated), while ECF, EOF, and EOX had 9.1%, 6.8%, and 6.3%, respectively [8]. A large retrospective study examined the rate of both arterial and venous thromboembolisms in 932 patients who were treated with cisplatin-based therapies and found an 18.1% incidence of thromboembolic events within 4 weeks of treatment. Of these, 92.7% were venous. In these patients on cisplatin therapy, apart from the Khorana score, age, performance status, and the presence of central venous, access devices were statistically associated with an increased risk of thrombosis [57]. Another recent study examined 129 patients being treated for advanced esophageal/gastric or junctional tumors with EXE (epirubicin, oxaliplatin, and capecitabine) and found an incidence of 16% (95% CI, 10–24%), with 21 VTE events in total. A majority of these patients had asymptomatic VTEs (68%), and increased tumor stage was associated with a higher risk of VTE [58].

Another systemic therapy agent perceived to be associated with increased thrombotic risk is bevacizumab, the anti-VEGF antibody used in colorectal and other cancers. A meta-analysis of 7956 patients in 15 randomized controlled trials of bevacizumab for various cancers found the overall incidence of venous thromboembolism in these patients at 11.9% (95% CI, 6.8–19.9%) with a relative risk of 1.33 (95% CI, 1.13–1.56) when compared with controls [59]. However, meta-analysis data suggest that exposure-adjusted incidence rates for venous thromboembolism with bevacizumab may not be significantly elevated compared to controls receiving chemotherapy. In one such analysis, 6055 patients on 10 randomized controlled trials of bevacizumab had a combined incidence rate of 18.5 events/100 patient years in contrast to 20.3/100 patient years for controls [60]. However, there is strong evidence suggesting bevacizumab can increase the risk of serious arterial thrombotic events in cancer patients [61].

Several other VEGF inhibitors such as sunitinib, sorafenib, and axitinib are known to increase the rate of arterial thrombotic events. A meta-analysis of trials found a 1.4% incidence of arterial thrombotic events and a relative risk of 3.03 (95% CI, 1.25–7.37) when compared with controls [62]. The mechanism for this increase in thrombotic risk is still a matter of investigation, and it has been postulated that VEGF inhibition can lead to increase in the hematocrit and viscosity due to increasing erythropoietin [63], by making endothelial cells more prone to damage [64], or by the independent activation of platelets through direct interaction [65].

Risk Assessment Models

In addition to the multiple clinical risk factors discussed earlier, several biomarkers of elevated thrombotic risk have been described in the literature (Table 21.1).

Given the multitude of risk factors and biomarkers, it is clear the etiology of cancer-associated thrombosis is multifactorial. In this context, a combination of multiple risk factors could better help stratify risk. Khorana et al. have validated a risk assessment model by using the easily available patient data comprising of platelet count, leukocyte count, and hemoglobin in combination with clinical characteristics in a large cohort of cancer patients. When combined as a risk score (Table 21.2)—with site of cancer (2 points for very-high-risk site, 1 point for high-risk site), a platelet count of 350 x 10^9/L or more (+1 point), hemoglobin less than 10 g/dL and/or use of erythropoiesis-stimulating agents (+1 point), leukocyte counts more than 11 x 10^9/L (+1 point), and a body mass index of 35 kg/m^2 or more (+1 point)—these scores predicted VTE rates in patients who are receiving outpatient chemotherapy. Rates of VTE in the derivation and validation cohorts were about 0.8% to 0.3% in low-risk (score = 0), 1.8% to 2% in an intermediate-risk (score = 1–2), and 7.1% to 6.7% in the high-risk (score ≥ 3) category over a median follow-up of 2.5 months [66]. This risk score was confirmed by the Vienna Cancer and Thrombosis Study (CATS). In addition, this group studied the use of soluble P-selectin (sP-selectin) and D-dimer to modify the risk score; however, this modified version has not yet been validated [67].

The Khorana score has since been validated in several other cohorts, such as in a retrospective cohort of patients treated with cisplatin where it was an independent predictor of VTE risk even after adjusting for other risk factors [57]. The Khorana score was also examined in a population of patients presenting for early phase I trials. In an analysis of

Table 21.1 Candidate biomarkers of cancer-associated thrombosis

Platelet count (≥350,000/mm^3)	Factor VIII
Leukocyte count (11,000/mm^3)	Prothrombin fragment F 1 + 2
Hemoglobin (<10 g/dL)	Activated partial thromboplastin time (aPTT) >30.8 seconds
D-dimer	
Tissue factor (TF) (expression, microparticles, antigen, or activity)	
Soluble P-selectin (53.1 ng/mL)	

Table 21.2 Risk assessment tool for prediction of cancer-associated thrombosis ("Khorana score")

Patient characteristics	Risk score
Site of cancer Very high risk (stomach, pancreas) High risk (lung, lymphoma, gynecologic, bladder, testicular)	2 1
Prechemotherapy platelet count 350,000/mm^3 or more	1
Hemoglobin level less than 10 g/dl or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11,000/mm^3	1
Body mass index 35 kg/m^2 or more	1

High-risk score ≥ 3
Intermediate-risk score = 1–2
Low-risk score = 0

the Southern Europe New Drugs Organization (SENDO) foundation data from 15 study centers, from the years 2000 to 2010, a total of 1415 patients presenting for phase I studies were analyzed for risk of VTE. Of these, 49.9% were on trials of cytotoxic therapies, while 22.2% of patients were on targeted therapies. In univariate analysis, the Khorana score, combination of antiangiogenic and cytotoxic agents, and time from cancer diagnosis were associated with a statistically significant increase of VTE. However, the multivariate analysis confirmed only a statistically significant association for the Khorana score, indicating that the score captures the risk from multiple variables. The hazard ratio of VTE occurrence was 7.88 (95% CI, 2.86–21.70) and 2.74 (95% CI, 1.27–5.92) times higher for the highest (≥3) and intermediate (1–2) scores as compared with score = 0 [68].

Studies of Thromboprophylaxis in Cancers, Including Gastrointestinal Cancers, and Prevention of Recurrent Events

Given the high prevalence and incidence of VTE in this setting, several trials have evaluated the benefit of thromboprophylaxis in patients with higher thrombotic risk (Table 21.3). Pancreatic cancer patients were a natural high-risk group to study. There are 3 randomized trials evaluating benefit of thromboprophylaxis with low-molecular-weight heparins (LMWHs) in the pancreas cancer population. These include the Charité – Onkologie (CONKO) and FRAGEM trials, and a trial from the MD Anderson Cancer Center.

In the CONKO-004 trial, investigators conducted a randomized controlled trial of ambulatory enoxaparin VTE prophylaxis in 312 patients with advanced pancreatic cancer. During the first 3 months, there was a decrease in the VTE incidence from 9.87% (15 of 152) in the observation arm to 1.25% (2 of 160) in patients who were on prophylactic enoxaparin for a hazard ratio of 0.12 (95% CI, 0.03–0.52). Overall cumulative incidence for VTE was 15.1% in the observation arm and 6.4% in the treatment arm. In terms of toxicity, 5 of 152 patients (3.3%) in the observation arm had major bleeding episodes in comparison with 7 of 160 (4.4%) in the treatment arm [69].

Another trial in this population, called the FRAGEM trial, was conducted in the UK where 123 patients with advanced pancreatic cancer who were being treated with gemcitabine were randomized 1:1 to dalteparin or placebo. Results were encouraging in this trial as well, with 23% rate of thrombosis in the observation arm and only 3.4% in the dalteparin arm, during the 12-week study period with an estimated relative risk of 0.145 (95% CI, 0.035–0.612). VTE risk through the entire study period was reduced from 28% to 12%. Importantly, the risk of major hemorrhagic events by International Society on Thrombosis and Haemostasis (ISTH) criteria was also similar (3% versus 3%), although the episodes of non-major bleeding by ISTM criteria were increased almost threefold in the dalteparin arm (9% versus 3%) [70].

Finally, a trial at the MD Anderson Cancer Center randomized 75 patients with advanced pancreatic cancer to dalteparin for 16 weeks during chemotherapy versus placebo in a 1:1 ratio. Patients were assessed for VTE events with screening ultrasounds at 8 and 16 weeks of treatment. Of patients in the control arm, 22% had VTE compared to 5% in the dalteparin arm, with an odds ratio of 0.014 (95% CI, 0.00–0.62) [71].

While these trials have evaluated the role of thromboprophylaxis in the very-high-risk population of advanced pancreatic cancer patients, several other trials have also evaluated the value of prophylaxis in the general population of cancer patients. For example, the Prophylaxis of Thromboembolism During Chemotherapy (PROTECHT) trial randomized 1150 patients in a 2:1 ratio to treatment with nadroparin (LWMH) versus placebo, respectively. These patients had a combination of various cancers, including pancreatic, gastrointestinal malignancies, lung, brain, breast, ovarian cancer, and cancers of the head and neck. At study completion, 2% of patients in the prophylaxis group developed VTE versus 3.9% in the placebo group. There did not appear to be large differences in the risk of bleeding with 0.7% incidence of major bleeding in the prophylaxis group compared to none in the placebo group, and 7.4% incidence of minor bleeding in the treatment group versus 7.9% in the placebo group [72].

Similarly, in the SAVE-ONCO trial, 3200 patients with locally advanced or metastatic adenocarcinomas were randomized to receive either semuloparin sodium (an ultra-low-molecular-weight heparin) or placebo. While there was clearly a statistically significant benefit with reduction of VTE with a hazard ratio of 0.36, there was also an increase in the bleeding risk with a hazard ratio of 1.4. The absolute measure of VTE risk was reduced from 3.4% to 1.2% on the overall analysis, and a look at data from the higher risk gastrointestinal cancers shows considerable absolute benefit. The hazard ratio for the pancreatic cancer group was 0.22 (2.4% in treatment group versus 10.9% in placebo); the hazard ratio was similarly lower

Table 21.3 Selected trials of VTE treatment and prophylaxis in cancer patients

Study name	Study population	Study design	Comparison group	VTE risk in prophylaxis group	VTE risk in control group	Benefit measure	Bleed risk prophylaxis	Bleed risk control	Risk measure	Year
Primary prophylaxis for VTE										
Pancreatic cancer										
CONKO 004	Advanced pancreatic cancer	Randomized controlled trial	Enoxaparin vs placebo	14.50%	5%	65% relative risk reduction (RRR)	6.30%	9.90%	n/s	2009
FRAGEM	Advanced pancreatic cancer	Randomized controlled trial	Dalteparin vs placebo	3.40%	23%	Relative risk [RR] 0.14 (0.187–0.935)	3% (major) 9% (minor)	3% (major), 3% (minor)	n/s	2012
MDACC	Advanced pancreatic cancer	Randomized controlled trial	Dalteparin vs placebo	5.00%	22%	Odds ratio [OR] 0.014 (0.00–0.62)	–	–	–	2013
General Cancer population										
SAVE-ONCO	Locally advanced/ metastatic solid tumors	Double blind multicenter RCT	Semuloparin vs placebo	1.20%	3.40%	Hazard ratio [HR] 0.36 (95% CI, 0.21–0.60)	2.80%	2.00%	HR, 1.40; 95% CI, 0.89–2.21	2012
PHACS	High-risk patients with cancer, Khorana score > =3	Randomized controlled trial	Dalteparin vs observation	12%	21%	Hazard ratio [HR] 0.69 (95% CI, 0.23–1.89)	14% (minor)	2.10%	Hazard ratio[HR] 7.0 (95% CI, 1.2–131.6)	
MicroTEC	Patients with cancer, stratified by TF levels	Phase II RCT	Enoxaparin vs observation	5.60%	27.2% (high-risk control), 7.2% (low-risk control)	(inverse) Hazard ratio [HR] 6.70 (95% CI, 1.03–43.17)	–	–	–	2013
Prophylaxis of recurrent VTE										
CATCH	Patients with cancer and h/o VTE	Multicenter randomized controlled trial	Tinzaparin vs warfarin	7.2% (for recurrence)	10.5% (for recurrence)	Hazard ratio [HR] 0.65; 95% CI, 0.41–1.03; $P = 0.07$	2.9% (major), 11% (minor)	2.7% (major), 17% (minor)	HR 0.89 [95% CI, 0.40–1.99] (major bleeding)	2014
CLOT	Patients with cancer and h/o VTE	Multicenter randomized controlled trial	Dalteparin vs oral coumarin derivative	9% (recurrence)	17% (recurrence)	Hazard ratio [HR] 0.48; 95% CI, 0.30–0.77	6% (major), 8% (minor)	4% (major), 15% (minor)	n/s	2003

at 0.25 with stomach cancer as well (0.5% in treatment group versus 1.9% in placebo); and the colorectal cancer group had a hazard ratio of 0.54 (1.1 with treatment versus 2.0% in placebo). However, the study was not powered to have statistical significance for the relatively low number of events in these disease subgroups except for pancreatic cancer [73].

Results of the PHACS (Prospective Randomized Multicenter Study of Dalteparin Prophylaxis in High-Risk Ambulatory Cancer Patients) trial were recently presented. This trial selected high-risk patients based on a Khorana score ≥ 3, and if negative for VTE on the initial screening, patients were randomized to dalteparin prophylaxis versus placebo and then followed for 12 weeks; 98 patients were eventually analyzed. Pancreatic, gastroesophageal cancers, lung, and lymphoma were the most common pathologies. Of patients in the dalteparin arm, 12% had VTEs compared with 21% of patients in the observation arm for a hazard ratio of 0.69 (95% CI, 0.23–1.89). Bleeding risk was higher with dalteparin compared to observation (hazard ratio of 7.0, 95% CI, 1.2–131.6). While these results are in line with the previously described studies, the results were not significant due to incomplete accrual and lack of statistical power [74].

Despite the evidence that thromboprophylaxis leads to risk reduction for VTE without increase in major bleeding episodes, the generally lower absolute risks and absolute risk reduction have been a reason for slow uptake and lack of positive recommendations on thromboprophylaxis. As a result, several newer approaches are being evaluated in both patient selection and therapeutic strategies for thromboprophylaxis in cancer patients to better identify higher-risk patients and/or to employ lower-risk treatments. In a recent phase II trial called the MicroTEC study (Microparticles and Thromboprophylaxis with Enoxaparin in Cancer), patients were stratified into high versus lower risk of VTE on the basis of circulating levels of tissue factor microparticles. Of a total of 66 patients evaluated, 32 patients had lower levels of TF-MPs, and 34 had high TF-MPs. Of the high-risk patients, 23 patients received enoxaparin prophylaxis, while 11 were observed. The study population was comprised of a majority of gastrointestinal tumors (pancreatic 30 of 66, colorectal 15 of 66). At 2 months, of patients with high TF-MP levels, 27.2% of patients on observation developed VTEs, compared to only 5.6% of patients on enoxaparin prophylaxis for a hazard ratio of 6.70 (95% CI, 1.03–43.17) [75]. In this study there were no bleeding events ascribed to enoxaparin. This study opens the door for a promising adjunct biomarker for classifying patients into high risk and may have particular significance for gastrointestinal cancers.

Newer-generation anticoagulants are also being evaluated in these populations. A currently ongoing pilot study will evaluate a combination of aspirin and statin to evaluate decrease in sP-selectin levels as a biomarker of thrombotic risk (NCT02285738). Another currently ongoing study called the Apixaban for the Prevention of Venous Thromboembolism in Cancer Patients (AVERT) study will evaluate one of the safest newer-generation oral anticoagulant, apixaban, in patients with high thrombosis risk defined by Khorana scores ≥2. A total of 574 patients are being recruited across 7 centers in Canadian hospitals, and randomization will occur between apixaban and placebo. VTE rates are to be compared at 7 months (NCT02048865). The CASSINI study will evaluate rivaroxaban for VTE prevention in cancer patients at high risk for thrombosis as defined by a Khorana score of ≥2, and is recruiting an estimated 700 participants. The study is expected to be completed by September 2018. In this study patients will receive thromboprophylaxis for 180 days while being initiated on chemotherapy for their cancer diagnosis (NCT02555878).

With the subject of thromboprophylaxis a matter of intense investigation, current uniform recommendations from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) suggest VTE prophylaxis only in patients with cancer who are hospitalized and for patients who have an established VTE for preventing recurrences, as described earlier. There are some additional special situations, such as patients being planned for major abdominal surgery, extremely high-risk patients, and patients receiving highly thrombogenic treatments for myeloma. A summary of the current recommendations of the ASCO guidelines committee is provided in Table 21.4.

Table 21.4 Recommendations for prophylaxis of cancer-associated thrombosis from ASCO

Patients with cancer should be periodically assessed for VTE risk using the Khorana score
Oncology professionals should educate patients about the signs and symptoms of VTE
Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization. Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion
Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high-risk patients
Patients with multiple myeloma receiving imid-based regimens with chemotherapy and/or dexamethasone should receive prophylaxis with either low-molecular-weight heparin (LMWH) or low-dose aspirin to prevent venous thromboembolism (VTE)
Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7–10 days
Extending postoperative prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features

Treatment of Venous Thromboembolism in Cancer Patients

Although the subject of thromboprophylaxis remains controversial, in the setting of a first episode of VTE, there is strong clinical data on the benefit of anticoagulation. It is generally accepted that without any specific contraindications, LMWHs are the most effective agents in this setting. This evidence is supported by a large, open-label, randomized controlled trial conducted around 1999–2001, where 676 patients who had a VTE event were placed either on dalteparin (a LMWH) or oral treatment with a coumadin analogue. Almost 90% of patients had a solid tumor, and most patients had metastatic disease. Dalteparin had a much superior efficacy with 9% recurrence on drug versus 17% with no significant differences in bleeding rates.

A large, multicenter, randomized controlled trial called the Comparison of Acute Treatments in Cancer Haemostasis (CATCH) study was recently concluded, which again reaffirmed the superiority of LMWH therapy. In this study, 900 patients from multiple sites across 32 countries were randomized to receive tinzaparin for VTE recurrence in comparison to warfarin. Study patients had multiple solid tumors, including colorectal (14.7%) and upper GI cancers (12.5%). In this study there was a trend for superiority with tinzaparin in prevention of VTEs (7.2% versus 10.5%) (HR 0.65 [95% CI, 0.41–1.03]; $P = 0.07$) with a comparable rate of major bleeding but a superior safety profile for clinically relevant bleeding (11% vs 17%) (HR, 0.58 [95% CI, 0.40–0.84]; $P = 0.004$) [76].

While the new evidence continues to be evaluated and incorporated into clinical practice, the ASCO guidelines committee provides the most current practice guidelines on the treatment of venous thromboembolism in cancer patients. A summary of key recommendations is provided in Table 21.5.

Table 21.5 Recommendations for treatment of cancer-associated thrombosis from ASCO

LMWH is recommended for the initial 5–10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months.
Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE.
Anticoagulation should not be used to extend survival of patients with cancer in the absence of other indications.

Conclusions and Future Directions

Thromboembolism remains a major cause of morbidity and mortality in patients with gastrointestinal cancers, and its impact is likely to increase with improving survival and outcomes in this patient population. Much has been learned about the mechanisms, pathophysiology, risk prediction, prevention, and treatment of this complication in the past decades. The next few years are likely to see greater progress in these areas. The advent of patient-friendly novel oral agents will likely see greater adoption of prophylaxis and treatment regimens. The availability of risk tools and predictive biomarkers could lead to risk-adapted approaches to both prevention and treatment. Continued work in this area along with continued education of both patients and clinical providers about this important complication of malignancy is essential to reduce the burden and consequences of cancer-associated thrombosis.

Acknowledgments Dr. Khorana acknowledges research support from the Sondra and Stephen Hardis Chair in Oncology Research and the Scott Hamilton CARES Initiative.

References

1. Lillicrap D. Introduction to a series of reviews on cancer-associated thrombotic disease. Blood. 2013;122(10):1687–8.
2. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost (JTH). 2006;4(3):529–35.
3. Khorana AA, O'Connell C, Agnelli G, Liebman HA, Lee AY, Subcommittee on H, et al. Incidental venous thromboembolism in oncology patients. J Thromb Haemost (JTH). 2012;10(12):2602–4.
4. Singh R, Sousou T, Mohile S, Khorana AA. High rates of symptomatic and incidental thromboembolic events in gastrointestinal cancer patients. J Thromb Haemost (JTH). 2010;8(8):1879–81.
5. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715–22.
6. SEER. Seer fact sheets. 2015 [cited 2015]; Available from: http://seer.cancer.gov/statfacts/.
7. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med. 2006;119(1):60–8.
8. Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F, et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK national cancer research institute upper gastrointestinal clinical studies group. J Clin Oncol. 2009;27(23):3786–93.

9. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using medicare claims data. Medicine. 1999;78(5):285–91.
10. Mark D. Danese MLG, Wendy J. In Langeberg JK, Kelsh MA, editors. Prevalence and incidence of comorbidities associated with gastric cancer ASCO GI cancers symposium; 2014.
11. Kang MJ, Ryoo BY, Ryu MH, Koo DH, Chang HM, Lee JL, et al. Venous thromboembolism (VTE) in patients with advanced gastric cancer: an Asian experience. Eur J Cancer. 2012 Mar;48(4):492–500.
12. Baek-Yeol Ryoo M-HR, Park SR, Kang MJ, Park K-O, Kim JH, Kang Y-K. Incidence and risk factors of thromboembolism (TE) in advanced gastric cancer (AGC) receiving chemotherapy: a prospective observational study (nct01047618). ASCO GI symposium; 20142014. p. abs 31.
13. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer – a cohort study using linked United Kingdom databases. Eur J Cancer. 2013;49(6):1404–13.
14. Menapace LA, Peterson DR, Berry A, Sousou T, Khorana AA. Symptomatic and incidental thromboembolism are both associated with mortality in pancreatic cancer. Thromb Haemost. 2011;106(2):371–8.
15. Blom JW, Osanto S, Rosendaal FR. High risk of venous thrombosis in patients with pancreatic cancer: a cohort study of 202 patients. Eur J Cancer. 2006;42(3):410–4.
16. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol (WJG). 2006;12(47):7561–7.
17. Yamashita Y, Bekki Y, Imai D, Ikegami T, Yoshizumi T, Ikeda T, et al. Efficacy of postoperative anticoagulation therapy with enoxaparin for portal vein thrombosis after hepatic resection in patients with liver cancer. Thromb Res. 2014;134(4):826–31.
18. Pirisi M, Avellini C, Fabris C, Scott C, Bardus P, Soardo G, et al. Portal vein thrombosis in hepatocellular carcinoma: age and sex distribution in an autopsy study. J Cancer Res Clin Oncol. 1998;124(7):397–400.
19. Ogren M, Bergqvist D, Bjorck M, Acosta S, Eriksson H, Sternby NH. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. World J Gastroenterol (WJG). 2006;12(13):2115–9.
20. Takizawa D, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, et al. Hepatocellular carcinoma with portal vein tumor thrombosis: clinical characteristics, prognosis, and patient survival analysis. Dig Dis Sci. 2007;52(11):3290–5.
21. Connolly GC, Chen R, Hyrien O, Mantry P, Bozorgzadeh A, Abt P, et al. Incidence, risk factors and consequences of portal vein and systemic thromboses in hepatocellular carcinoma. Thromb Res. 2008;122(3):299–306.
22. Jeon HK, Kim DU, Baek DH, Ha DW, Lee BE, Ryu DY, et al. Venous thromboembolism in patients with cholangiocarcinoma: focus on risk factors and impact on survival. Eur J Gastroenterol Hepatol. 2012;24(4):444–9.
23. Larsen AC, Brondum Frokjaer J, Wishwanath Iyer V, Vincents Fisker R, Sall M, Yilmaz MK, et al. Venous thrombosis in pancreaticobiliary tract cancer: outcome and prognostic factors. J Thromb Haemost (JTH). 2015;13(4):555–62.
24. Alcalay A, Wun T, Khatri V, Chew HK, Harvey D, Zhou H, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol. 2006;24(7):1112–8.
25. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001275.
26. Al-Shamsi HO, Al Farsi A, Shen H, Linkins L-A, Cook RJ, Major P, editors. Thrombotic events in patients with metastatic colorectal cancer treated with folfiri plus bevacizumab. ASCO GI cancer symposium 2013.
27. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer. 2013;119(3):648–55.
28. Walker AJ, West J, Card TR, Humes DJ, Grainge MJ. Variation in the risk of venous thromboembolism in people with colorectal cancer: a population-based cohort study from England. J Thromb Haemost (JTH). 2014;12(5):641–9.
29. Iversen LH, Thorlacius-Ussing O. Relationship of coagulation test abnormalities to tumour burden and postoperative DVT in resected colorectal cancer. Thromb Haemost. 2002;87(3):402–8.
30. Bergqvist D. Venous thromboembolism: a review of risk and prevention in colorectal surgery patients. Dis Colon Rectum. 2006;49(10):1620–8.
31. McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the Canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. Ann Surg. 2001;233(3):438–44.
32. Cole M, Bromberg M. Tissue factor as a novel target for treatment of breast cancer. Oncologist. 2013;18(1):14–8.
33. Shigemori C, Wada H, Matsumoto K, Shiku H, Nakamura S, Suzuki H. Tissue factor expression and metastatic potential of colorectal cancer. Thromb Haemost. 1998;80(6):894–8.
34. Alok A, Khorana SAA, Ryan CK, Francis CW, Hruban RH, Hu YC, Hostetter G, Harvey J, Taubman MB. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res. 2870;2007:13.
35. Nakasaki T, Wada H, Shigemori C, Miki C, Gabazza EC, Nobori T, et al. Expression of tissue factor and vascular endothelial growth factor is associated with angiogenesis in colorectal cancer. Am J Hematol. 2002;69(4):247–54.
36. Falanga A, Schieppati F, Russo D. Cancer tissue procoagulant mechanisms and the hypercoagulable state of patients with cancer. Semin Thromb Hemost. 2015;41(7):756–64.
37. Khorana AA, Ahrendt SA, Ryan CK, Francis CW, Hruban RH, Hu YC, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res. 2007;13(10):2870–5.
38. Thaler J, Koder S, Kornek G, Pabinger I, Ay C. Microparticle-associated tissue factor activity in patients with metastatic pancreatic cancer and its effect on fibrin clot formation. Transl Res. 2014;163(2):145–50.
39. Thomas GM, Brill A, Mezouar S, Crescence L, Gallant M, Dubois C, et al. Tissue factor expressed by circulating cancer cell-derived microparticles drastically increases the incidence of deep vein thrombosis in mice. J Thromb Haemost (JTH). 2015;13(7):1310–9.
40. Garnier D, Magnus N, Lee TH, Bentley V, Meehan B, Milsom C, et al. Cancer cells induced to express mesenchymal phenotype release exosome-like extracellular vesicles carrying tissue factor. J Biol Chem. 2012;287(52):43565–72.
41. Yamashita H, Kitayama J, Ishikawa M, Nagawa H. Tissue factor expression is a clinical indicator of lymphatic metastasis and poor prognosis in gastric cancer with intestinal phenotype. J Surg Oncol. 2007;95(4):324–31.
42. Hargett LA, Bauer NN. On the origin of microparticles: from "platelet dust" to mediators of intercellular communication. Pulm Circ. 2013;3(2):329–40.
43. Bastida E, Escolar G, Ordinas A, Jamieson GA. Morphometric evaluation of thrombogenesis by microvesicles from human tumor cell lines with thrombin-dependent (U87MG) and adenosine diphosphate-dependent (SKNMC) platelet-activating mechanisms. J Lab Clin Med. 1986;108(6):622–7.

44. Heinmoller E, Weinel RJ, Heidtmann HH, Salge U, Seitz R, Schmitz I, et al. Studies on tumor-cell-induced platelet aggregation in human lung cancer cell lines. J Cancer Res Clin Oncol. 1996;122(12):735–44.
45. Boukerche H, Berthier-Vergnes O, Penin F, Tabone E, Lizard G, Bailly M, et al. Human melanoma cell lines differ in their capacity to release ADP and aggregate platelets. Br J Haematol. 1994;87(4):763–72.
46. Sakai H, Suzuki T, Takahashi Y, Ukai M, Tauchi K, Fujii T, et al. Upregulation of thromboxane synthase in human colorectal carcinoma and the cancer cell proliferation by thromboxane A2. FEBS Lett. 2006;580(14):3368–74.
47. Ay C, Simanek R, Vormittag R, Dunkler D, Alguel G, Koder S, et al. High plasma levels of soluble p-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna cancer and thrombosis study (CATS). Blood. 2008;112(7):2703–8.
48. Chen M, Geng JG. P-selectin mediates adhesion of leukocytes, platelets, and cancer cells in inflammation, thrombosis, and cancer growth and metastasis. Arch Immunol Ther Exp. 2006;54(2):75–84.
49. Qi C, Li B, Guo S, Wei B, Shao C, Li J, et al. P-selectin-mediated adhesion between platelets and tumor cells promotes intestinal tumorigenesis in Apc(Min/+) mice. Int J Biol Sci. 2015;11(6):679–87.
50. Basu A, Gosain R, Tantry U, Miller K, Gurbel P. Platelet activation and aggregation in patients with advanced adenocarcinoma undergoing chemotherapy: correlation with a validated venous thromboembolism risk score. Blood. 2015;126(23):3445.
51. Ancrile B, Lim KH, Counter CM. Oncogenic Ras-induced secretion of il6 is required for tumorigenesis. Genes Dev. 2007;21(14):1714–9.
52. Phan VT, Wu X, Cheng JH, Sheng RX, Chung AS, Zhuang G, et al. Oncogenic RAS pathway activation promotes resistance to anti-VEGF therapy through G-CSF-induced neutrophil recruitment. Proc Natl Acad Sci U S A. 2013;110(15):6079–84.
53. Ades S, Kumar S, Alam M, Goodwin A, Weckstein D, Dugan M, et al. Tumor oncogene (KRAS) status and risk of venous thrombosis in patients with metastatic colorectal cancer. J Thromb Haemost (JTH). 2015;13(6):998–1003.
54. Wahrenbrock M, Borsig L, Le D, Varki N, Varki A. Selectin-mucin interactions as a probable molecular explanation for the association of trousseau syndrome with mucinous adenocarcinomas. J Clin Invest. 2003;112(6):853–62.
55. D'Asti E, Magnus N, Meehan B, Garnier D, Rak J. Genetic basis of thrombosis in cancer. Semin Thromb Hemost. 2014 Apr;40(3):284–95.
56. Licciardello JT, Moake JL, Rudy CK, Karp DD, Hong WK. Elevated plasma von Willebrand factor levels and arterial occlusive complications associated with cisplatin-based chemotherapy. Oncology. 1985;42(5):296–300.
57. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol. 2011;29(25):3466–73.
58. Larsen AC, Frokjaer JB, Fisker RV, Iyer V, Mortensen PB, Yilmaz MK, et al. Treatment-related frequency of venous thrombosis in lower esophageal, gastro-esophageal and gastric cancer–a clinical prospective study of outcome and prognostic factors. Thromb Res. 2015;135(5):802–8.
59. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA. 2008;300(19):2277–85.
60. Hurwitz HI, Saltz LB, Van Cutsem E, Cassidy J, Wiedemann J, Sirzen F, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. J Clin Oncol. 2011;29(13):1757–64.
61. Patel JN, Jiang C, Hertz DL, Mulkey FA, Owzar K, Halabi S, et al. Bevacizumab and the risk of arterial and venous thromboembolism in patients with metastatic, castration-resistant prostate cancer treated on Cancer and Leukemia group B (CALGB) 90401 (alliance). Cancer. 2015;121(7):1025–31.
62. Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. J Clin Oncol. 2010;28(13):2280–5.
63. Tam BY, Wei K, Rudge JS, Hoffman J, Holash J, Park SK, et al. VEGF modulates erythropoiesis through regulation of adult hepatic erythropoietin synthesis. Nat Med. 2006;12(7):793–800.
64. Kilickap S, Abali H, Celik I. Bevacizumab, bleeding, thrombosis, and warfarin. J Clin Oncol. 2003;21(18):3542; author reply 3543.
65. Meyer T, Robles-Carrillo L, Robson T, Langer F, Desai H, Davila M, et al. Bevacizumab immune complexes activate platelets and induce thrombosis in FCGR2A transgenic mice. J Thromb Haemost (JTH). 2009;7(1):171–81.
66. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902–7.
67. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, et al. Prediction of venous thromboembolism in cancer patients. Blood. 2010;116(24):5377–82.
68. Mandala M, Clerici M, Corradino I, Vitalini C, Colombini S, Torri V, et al. Incidence, risk factors and clinical implications of venous thromboembolism in cancer patients treated within the context of phase I studies: the 'SENDO experience'. Ann Oncol. 2012;23(6):1416–21.
69. Pelzer U, Opitz B, Deutschinoff G, Stauch M, Reitzig PC, Hahnfeld S, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. J Clin Oncol. 2015;33(18):2028–34.
70. Maraveyas A, Waters J, Roy R, Fyfe D, Propper D, Lofts F, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer. 2012;48(9):1283–92.
71. Vadhan-Raj S, Zhou X, Varadhachary GR, Milind J, David Fogelman RS, Bueso-Ramos CE, Nguyen M, Wang X, Wolff RA, Abbruzzese JL, Overman MJ, editors. Randomized controlled trial of dalteparin for primary thromboprophylaxis for venous thromboembolism (VTE) in patients with advanced pancreatic cancer (APC): Risk factors predictive of vte. 55th ASH Annual Meeting and Exposition; 2013; New Orleans: Blood.
72. Agnelli G, Gussoni G, Bianchini C, Verso M, Mandala M, Cavanna L, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol. 2009;10(10):943–9.
73. Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, Mismetti P, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med. 2012;366(7):601–9.
74. Khorana AA, Francis CW, Kuderer NM, Carrier M, Ortel TL, Wun T, Peterson D, Iyer R, Lyman GH. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: a randomized trial. Blood Annual Meeting Abstracts. 2015;126(23):427.
75. Zwicker JI, Liebman HA, Bauer KA, Caughey T, Campigotto F, Rosovsky R, et al. Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the Microtec study). Br J Haematol. 2013;160(4):530–7.
76. Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA. 2015;314(7):677–86.
77. Lee AYY, Khorana AA. Ch 134. Cancer associated thrombosis. In: DeVita Jr VT, Lawrence TS, Rosenberg SA, DePinho RA, Weiberg RA, editors. DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology. 10th ed. Philadelphia: Wolters Kluwer Health; 2015. p. 1969–75.

Nutrition and Cachexia in Gastrointestinal Cancer Patients

22

Meltem Gülhan Halil, Mehmet Emin Kuyumcu, Ömer Dizdar, Zekeriya Ulger, and Suayib Yalcin

Introduction

Although a very common secondary diagnosis for gastrointestinal (GI) cancer patients is malnutrition, it is usually underappreciated or underestimated among healthcare professionals as a result of a low level of awareness. However, nutrition status has an important impact on quality of life (QoL) and sense of well-being in cancer patients; therefore, its significance to patients and families is very high.

Malnutrition and weight loss—which have prognostic significance—are prevalent in GI cancer patients [1–3]. Multiple factors, including response to the tumor and cancer treatments, contribute to malnutrition [4, 5]. Malnutrition in GI cancer patients often involves cancer cachexia, which is characterized by a chronic, progressive, involuntary weight loss and muscle wasting as a result of decreased nutrient intake and metabolic alterations due to the activation of systemic proinflammatory processes that cannot be completely reversed by conventional nutrition support [6, 7].

Malnutrition affects all aspects of oncology treatment including treatment response, toxicity, performance status, QoL, and overall survival [8, 9]. Therefore, a nutritional aspect including nutritional screening and nutritional support should be considered for all cancer patients.

M. G. Halil (✉) · M. E. Kuyumcu
Department of Internal Medicine, Division of Geriatrics, Hacettepe University School of Medicine, Altındag, Ankara, Turkey
e-mail: meltemgulhan.halil@hacettepe.edu.tr

Ö. Dizdar
Department of Medical Oncology, Hacettepe University Cancer Institute, Altındağ, Ankara, Turkey

Z. Ulger
Department of Internal Medicine, Division of Geriatrics, Gazi University School of Medicine, Gazi University Hospital, Besevler, Ankara, Turkey

S. Yalcin
Department of Internal Medicine, Division of Medical Oncology, Hacettepe University School of Medicine, Institute of Cancer, Altındağ, Ankara, Turkey

Cancer Cachexia

Definition and Prevalence of Cachexia

Cachexia is derived from the Greek words *kakos* and *hexis*, which means "bad condition." Cachexia is a complex devastating condition characterized by loss of skeletal muscle mass with or without loss of fat, resulting in progressive functional impairment, and cannot be counteracted by conventional nutritional support. By definition, involuntary weight loss of ≥5% over 6 months or ≥2% in the presence of body mass index (BMI) <20 or sarcopenia should be present [7]. It may be associated with many chronic/end-stage diseases, including cancer, heart failure, renal or hepatic failure, chronic infections, or other inflammatory disorders. The pathogenesis is negative protein and energy balance through metabolic and endocrine alterations in addition to reduced food intake. Anorexia-cachexia in cancer patients is not synonymous with starvation. Many cancer patients have reduced food intake because of gastrointestinal obstruction, depression, or therapy-induced nausea, and this can be reversed with nutritional support and effective anticancer therapy. However, the benefit of nutritional support is limited in cachexia of patients with advanced cancer. Prevalence of cachexia varies according to cancer type; the incidence is more than 80% in upper GI cancers. The prevalence is highest in pancreatic cancer (88.9%), followed by gastric cancer (76.5%), esophageal cancer (52.9%), and colon cancer (50%) [10, 11].

Cancer cachexia is associated with worse survival as well as compromised quality of life [8]. The clinical spectrum ranges from pre-cachexia with minimal weight loss to severe refractory cachexia with low performance status and short life expectancy [12]. Anorexia, fatigue, reduced exercise capacity, and physical activity progressively impair the

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_22

patient's level of independence. Subsequent immobility and lethargy results in depression and isolation. Malnutrition is associated with increased risk of infections, falls, fractures, pressure ulcer development, and impaired quality of life [13]. Tolerance to chemotherapy is also reduced and complications are increased [12]. Finally, it is estimated that cachexia accounts for 20% of cancer deaths [13].

Assessment of Cachexia

Recent studies in various cancers showed improved treatment tolerance and quality of life with early nutritional intervention in patients with early-stage cachexia. Therefore, accurate assessment of the patient for the presence of cachexia signs is crucial. In one study, the false negativity rate in the diagnosis of cachexia among oncology physicians was 76% [10], delineating the need for standardized diagnostic tools. Asking patients about weight loss is the simplest and best validated method for assessment of nutritional status in daily practice. Patient-reported history of >5% weight loss was associated with shorter overall survival in multivariate analysis in patients treated within 12 Eastern Cooperative Oncology Group (ECOG) trials [2]. There are several methods introduced to assess the symptom burden, including loss of appetite, dysgeusia, constipation, early satiety, nausea, and vomiting. There is no consensus among the experts upon the best way of screening the nutritional status of cancer patients. The Nutritional Risk Screening 2002 (NRS 2002) is a validated tool to distinguish patients with nutritional risk who benefit from nutrition intervention from those who showed no benefit of nutrition support. NRS 2002 consists of a nutritional score and a severity of disease score and an age adjustment for patients >70 years [14]. The Edmonton Symptom Assessment Scale questions multiple symptoms including appetite and nausea [15]. The Patient-Generated Subjective Global Assessment (PG-SGA) also examines food intake, weight loss, and other nutritional symptoms including nausea, vomiting, constipation, mouth sores, pain, etc. The abridged Patient-Generated Subjective Global Assessment (aPG-SGA) is a modification of the original PG-SGA, and consists of a 4-part questionnaire that scores a patient's weight history, food intake, appetite, and performance status. It was recently validated in patients with cancer and it is easy to complete [16]. Detailed questionnaires provide good data for clinical trials but are difficult to perform for patients and healthcare providers in daily practice.

Dual-energy X-ray absorptiometry (DEXA) scan or computerized tomography (CT) can be used to assess fat and lean body mass composition, and identify patients with early sarcopenia. Overweight or obese patients with muscle wasting have poorer prognosis and cannot be identified with physical examination alone. DEXA is easy to perform and CT is already used for staging and response assessment in patients with cancer, and both tools may aid in the evaluation of cachexia and making treatment decisions [17]. Bioimpedance analysis (BIA) is a noninvasive method for estimation of body composition based on the principle that electric current flows at different rates through the body depending upon its composition [18]. It is quick and simple but not as accurate as DEXA or CT.

Mechanism for Cachexia

Anorexia alone cannot cause cachexia. It is the systemic inflammation-induced hypermetabolic (catabolic) state that causes the devastating condition (Fig. 22.1). There is an enormous increase in skeletal muscle proteolysis. Skeletal muscle protein breakdown is mainly controlled by ubiquitin-proteosome and autophagolysosomal pathways. In the ubiquitine-proteosome system, a chain of ubiquitin is attached covalently to the proteins and they are targeted for degradation by the 26 s proteosome. The most important ubiquitin ligases in cancer cachexia are Atrogin-1/Mafbx and Murf1 [19]. Autophagy is a catabolic process in which damaged macromolecules and organelles are degraded within the cell. Autophagy is activated in muscles of tumor-bearing animals and might contribute to muscle wasting associated with cachexia [20]. These pathways are essentially regulated by different transcriptional signals in healthy and disease states. For example, it is hypothesized that abnormal production of inflammatory cytokines such as tumor necrosis factor (TNF) and interleukine 6 (IL-6) suppress the appetite and activate the ubiquitine-proteosome pathway, which subsequently results in muscle tissue breakdown. Proteolysis-inducing factor (PIF) is found in the serum and urine of patients with various cancers and cachexia [21]. PIF increases messenger RNA (mRNA) levels of ubiquitin carrier protein and proteosome subunits and activates transcription factor NF-KB, subsequently resulting in muscle protein degradation. PIF also inhibits protein synthesis by activation of the RNA-dependent protein kinase [22]. Myostatin and activins are other mediators that promote muscle loss in cancer cachexia by upregulating Atrogin-1/Mafbx and Murf1 [23, 24]. Ring finger protein, a family of ubiquitin ligases, including muscle RING-finger protein-1 (MuRF1), has been proposed to trigger muscle protein degradation via ubiquitination. It is activated by NF-KB, PIF, and other cytokines that are already increased in patients with cachexia [25]. The mechanism behind adipose tissue loss is less clear. Zinc alpha2 glycoprotein is an adipokine that is upregulated in cancer cachexia and induces lipolysis and fat oxidation [26]. Other inflammatory mediators including TNF also increase lipolysis and decrease lipogenesis.

Energy homeostasis also has a tight neuroendocrine regulation, with the hypothalamus having the pivotal role. Various neurotransmitters including pro-opiomelanocortin, serotonin,

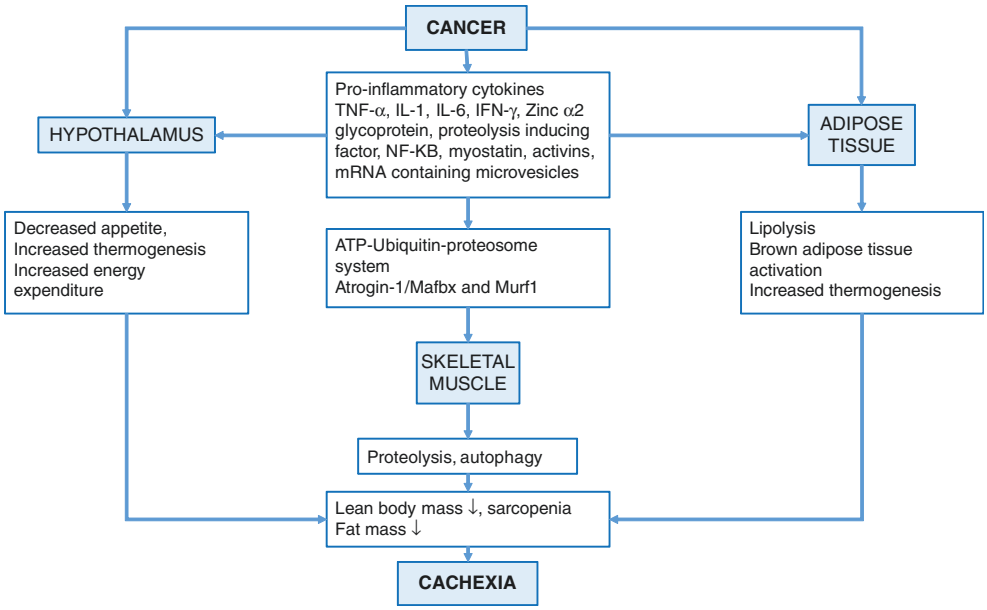


Fig. 22.1 Mechanism of cancer cachexia. Abbreviations: TNF tumor necrosis factor, IL interleukin, IFN interferon, NF-KB nuclear factor kappa b, ATP adenosine tri-phosphate, Murf1 muscle RING-finger protein-1, Mafbx muscle atrophy F-box

and dopamine have divergent roles in appetite regulation. Tumor-secreted cytokines also affect these hypothalamic neuronal cells and induce hypothalamus-mediated anorexia [25]. Ghrelin also attenuates muscle protein degradation and cachexia and improves food consumption through hypothalamic effects. Hypothalamus also mediates increased thermogenesis and skeletal muscle atrophy in cancer cachexia [27].

Interestingly, cancer cachexia increases energy expenditure in contrast to starvation, in which energy expenditure is decreased. This process is mediated by brown adipose tissue and coordinated by the hypothalamus [28, 29]. Increased oxidative stress and mitochondrial dysfunction are other important events associated with cachexia.

Recently, microRNAs (miRNAs) have been shown to have a role in the muscle-wasting process due to cachexia. Acunzo et al. found that muscle cachexia was associated with a high level of shedding of microvesicles containing mir21 from lung and pancreatic cancer cells. These microvesicles, which contain mRNAs derived from cancer cells, were discovered to fuse with myoblasts and induce skeletal muscle cell apoptosis [30]. These microvesicles were particularly active on myoblasts expressing TLR 7/8.

Management of Cachexia

Loss of appetite, inability to eat, and resulting weight loss are burdensome for the patient and the family. Most of the patients referred to nutritionists have advanced cachexia, which is often unresponsive to treatment. Therefore, all cancer patients should be screened for weight loss, nutritional status, and the presence of cachexia to identify potential candidates for nutritional support.

Table 22.1 Management of cachexia

Evaluation	Weight loss history Assessment of sarcopenia (DEXA/ CT/BIA) Nutritional screening (NRS-2002, PG-SGA/ aPG-SGA) Assessment of oral intake
Treatment of comorbidities	Depression Pain Xerostomia Constipation/motility problems Immobility – exercise
Nutritional support	Food fortification Oral nutritional supplements Tube feeding Parenteral/enteral nutrition
Pharmacotherapy of appetite and fatigue	Megestrol acetate Corticosteroids Cannabinoids Androgens/selective androgen receptor modulator Ghrelin/ghrelin receptor agonists Fish oil/eicosapentaenoic acid

DEXA Dual-energy X-ray absorptiometry, *CT* computed tomography, *BIA* bioelectric impedance analysis, *NRS* Nutritional Risk Screening, *PG-SGA* Patient-Generated Subjective Global Assessment, *aPG-SGA* Abridged Patient-Generated Subjective Global Assessment

Current management for cancer cachexia consists of identification and treatment of reversible metabolic abnormalities, nutritional support, appetite stimulants, anabolic agents, and anti-inflammatory agents (Table 22.1). Many cancer patients have depression, pain, dyspnea, xerostomia, constipation, gastrointestinal motility problems or obstruction, which are caused by the tumor itself, chemotherapy, or radiotherapy and may cause inadequate caloric intake and weight loss. Psychiatric consultation and antidepressants may improve depression and effective analgesic therapy

may reduce pain and improve oral intake [12, 31]. A phase II trial of mirtazapine, a tetracyclic antidepressant that may lead to weight gain, in patients with cancer-related cachexia/anorexia resulted in weight gain ≥1 kg at week 4 in 24% of the patients. Appetite and health-related quality of life (HQOL) were also improved [32]. Constipation may be induced by immobilization, narcotic analgesics, 5-HT3 antagonists, or obstruction. Treatment with dietary manipulation, laxatives, and dilatation/stenting for local GI obstruction when available may be useful in selected cases. Symptomatic agents such as metpamid improve GI motility, gastric emptying, and therefore appetite. Endocrine disorders including thyroid dysfunction, adrenal insufficiency or hypogonadism, vitamin and micronutrient deficiencies may also ameliorate appetite, fatigue, and dysgausea. Identification and treatment may result in improvement of cachexia [31]. Exercise should be recommended and may help to prevent or at least slow down the loss of skeletal muscle mass, strength, and physical function. Exercise was shown to reduce muscle proteolysis and mitochondrial dysfunction in animal models of cancer cachexia [33]. There are no randomized trials on the efficacy of exercise in patients with cachexia. However, the benefits of exercise on muscle mass, physical function, and even inflammation were previously shown [34, 35].

Patients should be counseled with a nutritionist and counseling should include symptom management, type and route of delivery of the nutritional support, food fortification, and self-monitoring.

Pharmacotherapy

Megestrol Acetate

Nutrition is essential but is usually not effective alone, and pharmacological treatment and other measures should also be considered. The only US Food and Drug Administration (FDA)-approved pharmacotherapy for the treatment of cachexia is megestrol acetate (MA). MA is a synthetic progestin that increases appetite and body weight [36]. The exact mechanism of action is unknown but it seems to reduce inflammatory cytokines and increase neuropeptide Y levels. Starting dose is 160 mg/d and improvement at appetite starts at this dose. Weight gain is observed at doses >400 mg/d. Megestrol acetate has serious side effects including venous thromboembolism, edema, dyspnea, and impotence. Prolonged use may further increase toxicity. Anti-anabolic effect may even result in muscle loss [37]. High doses were even associated with increased mortality. Stress dose corticosteroid use might be needed in acute illness or preoperatively, because these patients may have adrenal suppression. Therefore, patients should be informed about potential toxicities and minimum effective dose should be used in clinical practice.

Corticosteroids

Two small randomized studies demonstrated improvements in fatigue and appetite with dexamethasone and methylprednisolone, but no benefit on lean body mass was observed [38, 39]. Side effects including edema, candidiasis, depression, proximal muscle weakness, and anxiety preclude prolonged use. Dexamethasone is preferred because of its lower mineralocorticoid effect, and short-term use may be of benefit in terminal patients.

Cannabinoids

Dronabinol is approved for the treatment of anorexia in patients with acquired immunodeficiency syndrome (AIDS) but data on its use in cancer patients is limited. Two randomized studies did not show any difference in appetite compared to placebo and MA, respectively [40, 41]. Combination of MA and dronabinol also yielded no additional benefit. One recent trial showed improved appetite, caloric intake, and quality of life compared with placebo [42].

Fish Oil or Eicosapentaenoic Acid

A recent systemic review did not demonstrate a clear benefit of eicosapentaenoic acid (EPA) on body weight or lean tissue in cancer patients [43]. One recent randomized trial in patients with advanced non-small cell lung cancer showed 69% of patients in the fish oil group gained or maintained muscle mass. Comparatively, only 29% of patients in the placebo group maintained muscle mass [44]. Muscle weight loss was overall 1 kg in the placebo group.

Androgens

Testosterone replacement in male patients with advanced cancer and hypogonadism improved fatigue, but no effect was observed on appetite or weight [45]. Selective androgen receptor modulator enobosarm also improved lean body mass in patients with advanced cancer and cachexia [46].

Ghrelin and Ghrelin Receptor Agonists

Ghrelin is an orexigenic peptide hormone produced in the stomach and other parts of the GI tract. Ghrelin enhances appetite and food intake by binding its hypothalamic receptors, stimulates GI motility, reduces thermogenesis and energy consumption, and induces lipogenetic pathways. Ghrelin also increases insulin-like growth factor-1 (IGF-1) production and inhibits production of proinflammatory cytokines and prevents muscle atrophy by this way. Anamorelin is a potent orally active ghrelin receptor agonist with a longer half-life than ghrelin [27]. A phase II randomized study in patients with stage 3–4 non-small cell lung cancer showed a beneficial effect on body weight and improved quality of life with anamorelin 100 mg/d compared with 50 mg/d dose or placebo. No effect on overall survival was seen [47]. Another small phase II study also showed similar results with increased lean body mass (LBM) and total body mass with

anamorelin 50 mg compared with placebo [48]. Based on these results, 3 phase III randomized studies were conducted with anamorelin compared with placebo in patients with non-small cell lung cancer and cachexia. Anamorelin dose was 100 mg /day and was used for 12 weeks. At the end of a 12-week treatment period, participants were allowed to enroll in the ROMANA III trial, which was the extension trial of anamorelin to 24 weeks. Recently, the results of ROMANA I and II trials were reported and showed increased lean body mass, body weight, and improved appetite compared with placebo whereas handgrip strength was similar. Patients receiving anamorelin also experienced improvement in anorexia-cachexia symptoms as evaluated with the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Anamorelin was well tolerated with similar overall survival between the study arms. The most common grade 3–4 adverse events were fatigue, asthenia, atrial fibrillation, and dyspnea (5% each) [49]. The ROMANA III trial showed similar safety with prolonged use over 24 weeks [50]. Ghrelin was suggested to stimulate growth hormone and IGF-1 secretion and to potentially promote tumor growth, but no difference in tumor progression or death rates were observed in these trials.

Malnutrition in Gastrointestinal Cancer Patients

Prevalence of Malnutrition

Malnutrition, as a risk factor for increased morbidity and mortality, is frequent in gastrointestinal cancer patients. Nutrition management is really important, however, it remains insufficient in cancer patients [51]. The prevalence of weight loss and malnutrition ranged from 31% to 87% depending on the tumor site and stage, with the highest frequencies observed in patients with aerodigestive tract cancer or more advanced disease [2, 52, 53]. The incidence of disease-related malnutrition is 30–80% in hospitalized patients with cancer. Furthermore, it has been suggested that more than 20% of cancer patient mortality—directly or not—can be associated with malnutrition, rather than the malignant disease itself [54, 55]. At initial cancer diagnosis, approximately 50% of patients present with some nutritional issues. In gastric and pancreatic cancer, up to 85% of patients will develop malnutrition/weight loss during treatment [56].

Adverse Outcomes of Malnutrition

Malnutrition is the most underappreciated complication of gastrointestinal cancer and it has also been associated with prolonged hospital stay, increased readmissions to the hospital, increased frequency and severity of infections, poor wound healing, gait disorders, falls and fractures [8, 9, 57–59]. Unfortunately, nutritional awareness is low among medical practitioners because of lack of sufficient nutritional education in medical schools. However, the significance of malnutrition to cancer patients and families is very high and they may resort to using herbs, supplements, and pills; nutritional information is often specifically requested.

Patients with GI cancer are prone to malnutrition, due to loss of appetite, inability to ingest or absorb adequate calories, mucositis, and metabolic problems. Those patients are in a catabolic state and metabolic demands increase with anticancer treatment (surgery, chemotherapy, radiotherapy) and further worsen the problem [9, 60, 61].

The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines state that cancer patients are nutritionally-at-risk and should undergo nutrition screening to identify those who require formal nutrition assessment with development of a nutrition care plan [60, 61]. Studies show that the prognosis for cancer patients with weight loss is worse than weight-stable patients. Unintentional weight loss is also associated with treatment-related adverse reactions, low quality of life, bad response to cancer treatment, and a poor prognosis [9]. Weight loss is higher in patients with pancreatic, gastric, and lung cancer (83–87%) than other types of cancer [2]. Andreyev et al. showed in their study of 1555 patients with four major gastrointestinal cancers that the frequency of weight loss is nearly 70% and more frequent in men [8]. Weight loss also is associated with less therapy (both dose and duration), more drug toxicity, poor performance, poor life quality, lower response rate, and shorter overall survival [8]. Therefore, early detection and prevention of malnutrition is very important in patients with GI cancer. There is no conclusive data that show any effect of enteral nutrition (EN) on tumor growth [9].

Screening/Assessment of Malnutrition

Fifty-five percent of patients reported that their oral food intake had decreased since diagnosis with cancer, while 30% of the patients with a visual analog score (VAS) between 0 and 3 had not received any dietary advice and/or had been prescribed any oral nutritional supplements [53]. Systematic screening and care of malnutrition is an essential step in the global management of all cancer patients [60]. Different assessment methods have been used for nutritional evaluation of patients with GI cancer, with emphasis on anthropometry, biochemical data, and clinical and subjective evaluation [61, 62]. Screening of malnutrition must be performed systematically by the doctor, nurse, or dietitian. If the screening is positive, a more detailed investigation is needed. The screening tools are relatively similar, using parameters such as recent weight loss, recent poor intake/appetite, body mass index or body weight measures, and providing a numerical score to categorize risk of malnutrition. While choosing a screening tool it is important to ensure that it is easy and quick to perform and that it can screen all at-risk patients. Various

screening tools have been developed and validated for identifying patients at risk of malnutrition, but there is no gold standard for evaluating nutritional status. The most widely used screening tools are Nutrition Risk Screening 2002 (NRS-2002) [63], Malnutrition Universal Screening Tool (MUST) [61, 64], subjective global assessment (SGA) [65], and the Mini Nutritional Assessment (MNA) test [66].

NRS-2002 consists of a first screening stage (4 simple questions) followed by a second stage that assesses a patient's nutritional status and the severity of illness. This method has been validated and recognized by the European Society for Clinical Nutrition and Metabolism (ESPEN) and it was selected as the first choice for hospital inpatients [63, 67]. The MUST is a validated method and combines percentage unplanned weight loss, body mass index, and the effects of acute disease. It is suggested for screening of community-dwelling patients [64]. MNA is also a valid and effective screening method and ESPEN recommends MNA for nutritional evaluation of geriatric patients [66]. The SGA requires a physical examination by a health professional. Therefore, it is a time consuming but easy tool to use [65]. The PG-SGA was developed for cancer patients and includes a patient questionnaire in addition to the physical examination and was shown to effectively identify malnutrition [55, 68]. The PG-SGA, aPG-SGA, SGA, and nutritional risk index (NRI) have validated specificity and sensitivity in cancer patients, have been the subjects of prospective clinical trials, and share an emphasis on clinical data [16, 69, 70].

Anthropometric measurements including weight, height, limb circumferences (calf, mid-upper arm), and skinfold thicknesses are noninvasive techniques that provide information or estimation of body composition, fat, and muscle stores [71, 72]. Bioelectric impedance analysis, as a noninvasive and easily performed bedside technique of body composition analysis, may be a good alternative indicator of nutritional status [73]. Evaluation of the contribution of body composition measurements may give us fat mass and free-fat mass or lean body mass changes before weight loss. Thus, it provides early recognition of malnutrition [74]. Loss of lean body mass is associated with impaired immunity, increased infection, bad wound healing, weakness, pressure sores, and death—usually from pneumonia [57]. Additionally, evidence suggests that lean body mass may be useful to normalize doses of chemotherapy. Prado et al. demonstrated that low lean body mass is a significant predictor of toxicity in female patients administered 5-fluorouracil (5-FU) using the convention of dosing per unit of body surface area [75].

Phase angle measured by BIA may be a useful and sensitive indicator of malnutrition [76]. Depletion of body proteins or lower phase angle (different cut-offs for different cancer types) are also associated with a poorer survival in cancer patients [77].

Body composition measures, assessed by CT, were described as important predictors of nutritional status in patients with lung and colon cancers. Evaluation of images obtained from the third or fourth lumbar vertebra was assessed for adipose tissue, total lean tissue, and total muscle mass [78]. Dalal et al. showed that in 41 locally advanced pancreatic cancer patients treated with chemoradiation, 81% experienced weight loss; during this treatment, median loss of skeletal mass was 4%, visceral adipose tissue 13%, subcutaneous adipose tissue 11%, and age and higher visceral adipose tissue loss were correlated with survival [79]. Low subcutaneous and muscular fat is a sign of poor nutritional status in recent studies. If confirmed in larger studies, the use of CT for body composition measurements as indicators of nutritional status may become a useful tool for cancer patients [79].

Sarcopenia is a syndrome characterized by loss of muscle mass and strength with adverse outcomes such as physical disability, poor life quality, and death [80, 81]. In patients with metastatic colorectal cancer, sarcopenia was an independent predictor of worse recurrence-free and overall survival [82]. Levoger et al. demonstrated that sarcopenia identified before surgery by CT was associated with impaired overall survival in gastrointestinal and hepatopancreatobiliary malignancies, and increased postoperative morbidity in patients with colorectal cancer with or without hepatic metastases [83].

Some laboratory parameters, including albumin and prealbumin, are suitable for recognition of and intervention for malnutrition. Serum prealbumin is often used to assess adequacy of nutritional support more than albumin, given its shorter half-life of 2.5 days. However, prealbumin is a negative acute-phase protein and its synthesis decreases in patients with inflammation and cancer. C-reactive protein (CRP) is often used in combination with prealbumin to assess whether the changes in prealbumin are reflective of adequate nutrition support or changes in inflammation [62]. Albumin, creatinine, and urea were used for evaluation of malnutrition in some studies, but there is not yet enough data for routine recommendation.

Additionally, 1–3 day dietary record is a useful way of checking normal eating habits and amount of calories and protein consumption by GI cancer patients.

Fruchtenicht et al. evaluated more than 70 nutritional assessment tools that have been described and analyzed in different populations. None of the tools was considered as the gold standard for nutritional assessment in terms of sensitivity and specificity. They suggested that assessment should be performed by combining different methods and taking into account the limitations of each method [84].

Nutritional Support in Gastrointestinal Cancer Patients

Nutritional Requirements

ESPEN states that the nutritional goal in cancer patients is improvement of function and outcome by preventing and treating undernutrition, enhancing antitumor treatment

effects, reducing adverse effects of antitumor therapies, and improving quality of life [9].

Generally, the energy requirement of cancer patients is equal to normal healthy subjects [9]. In some studies, resting energy expenditure (REE), measured by indirect calorimetry, showed that in 25% of patients with active cancer REE is more than 10% higher, and in another 25% it is more than 10% lower than predicted energy expenditure [85]. Tumor types can affect the REE. REE is normal in patients with gastric or colorectal cancers and higher than expected in subjects with pancreatic cancers [86–88]. Other studies with pancreatic cancer patients demonstrated a relative increase in REE, while physical activity level and total energy expenditure (TEE) were decreased when compared to predicted values for healthy subjects [89]. The measurement of REE cannot be possible for all patients; therefore, TEE can be used for non-obese patients by using the actual body weight. ESPEN guidelines recommend a caloric intake of 30–35 kcal/kg/day for ambulatory patients and 20–25 kcal/kg/day for bedridden patients. But these recommendations are less favorable for severely underweight and severely overweight patients [9].

Standard enteral formulae are recommended for enteral nutrition of cancer patients. The recommended protein intake range for cancer patients is 1.2–2 g/kg/day. Lipids might be the preferred substrate for cancer patients, but there is no clear evidence in effectiveness. There is not enough data to suggest a cancer-specific enteral formula [90, 91].

Timing of Nutritional Support in Gastrointestinal Cancer Patients

It is hard to determine when to initiate nutritional support in gastrointestinal cancer patients. It is relatively easy in obviously malnourished patients with a curable cancer when they are unable to meet their nutritional needs for prolonged periods. Examples include patients with severe mucositis, dysphagia, or intestinal obstruction. All guidelines recommend early and complete nutritional support for such patients. However, the decision to intervene is more difficult when nutritional intake is closer to meeting needs, or when the likely period of inadequate intake is uncertain, or in incurable patients. In these settings, decision-making is more complex, and risk-benefit analysis should be done carefully, keeping in mind that nutrition support is not a procedure that is completely free of risk [7, 92].

General nutritional management recommendations are usually similar in all cancer patients. Table 22.2 [60] and Table 22.3 [9] summarize the guideline recommendations of ESPEN and ASPEN about nutritional evaluation and support

Table 22.2 ASPEN guideline recommendations on nutrition support during adult anticancer treatment [60]

ASPEN Guideline Recommendations	Grade
Nutrition support therapy during anticancer treatment	
1. Patients with cancer are nutritionally-at-risk and should undergo nutrition screening to identify those who require formal nutrition assessment with development of a nutrition care plan.	D
2. Nutrition support therapy should not be used *routinely* in patients undergoing major cancer operations.	A
3. Perioperative nutrition support therapy may be beneficial in moderately or severely malnourished patients if administered for 7–14 days preoperatively, but the potential benefits of nutrition support must be weighed against the potential risks of the nutrition support therapy itself and of delaying the operation.	A
4. Nutrition support therapy should not be used *routinely* as an adjunct to chemotherapy.	B
5. Nutrition support therapy should not be used *routinely* in patients undergoing head and neck, abdominal, or pelvic irradiation.	B
6. Nutrition support therapy is appropriate in patients receiving active anticancer treatment who are malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time	B
7. The palliative use of nutrition support therapy in terminally ill cancer patients is rarely indicated.	B
8. Omega-3 fatty acid supplementation may help stabilize weight in cancer patients on oral diets experiencing progressive, unintentional weight loss.	B
9. Patients should not use therapeutic diets to treat cancer.	E
10. Immune-enhancing enteral formulas containing mixtures of arginine, nucleic acids, and essential fatty acids may be beneficial in malnourished patients undergoing major cancer operations	A

Grading of Guidelines:
A – Supported by at least two level I investigations
B – Supported by one level I investigation
C – Supported by at least one level II investigations
D – Supported by at least one level III investigations
E – Supported by level IV or V evidence
Levels of Evidence:
I – Large randomized trials with clear-cut results; low risk of false-positive (alpha) and/or false-negative (beta) error
II – Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error
III – Nonrandomized cohort with contemporaneous controls
IV – Nonrandomized cohort with historical controls
V – Case series, uncontrolled studies, and expert opinion

Table 22.3 ESPEN guideline recommendations in nonsurgical oncology patients [9]

Subject	ESPEN guideline recommendations	Grade
General	1. Nutritional assessment of cancer patients should be performed frequently, and nutritional intervention initiated early when deficits are detected.	C
General	There are no reliable data that show any effect of enteral nutrition on tumor growth. Such theoretical considerations should, therefore, have no influence on the decision to feed a cancer patient.	C
Indication general	Start nutritional therapy if undernutrition already exists or if it is anticipated that the patient will be unable to eat for 4–7 days.	C
Indication general	Start enteral nutrition if an inadequate food intake (60% of estimated energy expenditure for 4–10 days) is anticipated. It should substitute the difference between actual intake and calculated requirements.	C
Indication general	In weight-losing patients due to insufficient nutritional intake enteral nutrition should be provided to improve or maintain nutritional status.	B
Perioperative	Patients with severe nutritional risk benefit from nutritional support 10–14 days prior to major surgery even if surgery has to be delayed.	A
During radiotherapy or radiochemotherapy	Use intensive dietary advice and oral nutritional supplements to increase dietary intake and to prevent therapy-associated weight loss and interruption of radiation therapy.	A
During radiotherapy or radiochemotherapy	Routine enteral nutrition is not indicated during radiation therapy.	C
During chemotherapy	Routine enteral nutrition during chemotherapy has no effect on tumor response to chemotherapy or on chemotherapy-associated unwanted effects and, therefore, is not considered useful.	C
During stem cell transplantation	The routine use of enteral nutrition is not recommended.	C
During stem cell transplantation	If oral intake is decreased, parenteral nutrition may be preferred to tube feeding in certain situations (i.e., increased risk of hemorrhage and infections associated with enteral tube placement in immunocompromised and thrombocytopenic patients).	C
Application	Prefer the enteral route whenever feasible.	A
Application	Administer preoperative enteral nutrition preferably before admission to the hospital.	C
Route	Use tube feeding if an obstructing head or neck or esophageal cancer interferes with swallowing or if severe local mucositis is expected.	C
During radiotherapy or radiochemotherapy	Tube feeding can either be delivered via transnasal or percutaneous routes. Because of radiation-induced oral and esophageal mucositis, a percutaneous gastrostomy (PEG) may be preferred.	C
Type of formula general	Use standard formulae.	C
Type of formula general	Regarding omega-3 fatty acids, randomized clinical trial evidence is contradictory/controversial, and at present, it is not possible to reach any firm conclusion with regard to improved nutritional status/physical function. It is unlikely that omega-3 fatty acids prolong survival in advanced cancer.	C
Perioperative	Use preoperative enteral nutrition preferably with immune-modulating substrates (arginine, omega-3 fatty acids, nucleotides) for 5–7 days in all patients undergoing major abdominal surgery independent of their nutritional status.	A
Drug treatment	In the presence of systemic inflammation, pharmacological efforts are recommended in addition to nutritional interventions to modulate the inflammatory response.	C
Drug treatment	In cachectic patients, steroids or progestins are recommended in order to enhance appetite, modulate metabolic derangements, and prevent impairment of quality of life.	A
Drug treatment	Administer steroids for short-term periods only, weighing their benefits against their adverse side effects.	C
Drug treatment	Consider the risk of thrombosis during progestin therapy.	C

ASPEN states that omega-3 fatty acid supplementation may help to stabilize weight in cancer patients on oral diets experiencing progressive, unintentional weight loss [60]. According to ESPEN, randomized clinical trial evidence is contradictory, so at present it is not possible to reach any firm conclusion with regard to improved nutritional status/physical function [9].

Enteral Versus Parenteral Nutrition

If the nutritional aims cannot be achieved by an oral route, tube feeding should not be delayed if there is no contraindication for its use. Tube feeding is not appropriate if there is mechanical intestinal obstruction due to cancer or surgical short bowel syndrome. In other words, for patients who need

in cancer patients. Moreover, these recommendations can easily be adapted for the patients with GI cancer.

If food intake is markedly reduced for ≥7 days or intake of under 60% of estimated energy expenditure for ≥10 days, ESPEN recommends a rapid implementation of nutritional support as a clinically appropriate intervention for cancer patients [9]. ASPEN recommends perioperative nutrition support therapy for moderately or severely malnourished patients for 7–14 days preoperatively [60]. Enteral nutritional support is recommended if the gastrointestinal tract is available and functional. Enteral nutrition should be provided to improve or maintain nutritional status in cancer patients who are losing weight due to inadequate nutritional intake. Additionally, enteral nutrition is indicated preoperatively for 5–7 days in cancer patients or 10–14 days in patients with severe malnutrition undergoing major abdominal surgery [9].

During radiotherapy or chemotherapy, suitable dietary implementations and oral nutritional supplements are advised to increase or maintain dietary intake and to prevent radiochemotherapy-associated weight loss and ultimately failure of these therapies [93, 94]. Routine enteral nutrition is not indicated during radiation therapy and chemotherapy [9, 60]. Enteral feeding using nasogastric or percutaneous tubes (e.g., percutaneous endoscopic gastrostomy) is recommended in radiation-induced severe mucositis or in obstructive tumors of the head-neck or thorax or in patients undergoing curative anticancer drug treatment, if oral food intake is inadequate despite counseling and oral nutritional supplements (ONS). Elia et al. concluded in their meta-analysis that in patients undergoing chemotherapy/radiotherapy, oral nutritional supplements or tube feeding had no additional positive effect on mortality when compared to routine care. It has to be assumed, however, that if response to antitumor treatment is lacking, stabilization of weight cannot be anticipated, since additive catabolic effects result from both the inflammatory response and the chemotherapy [95].

If oral intake is markedly decreased, parenteral nutrition (PN) may be preferred to tube feeding in certain situations, including increased risk of hemorrhage and infections associated with enteral tube placement in immunocompromised and thrombocytopenic patients [9].

ESPEN states that in incurable patients, enteral nutrition should be provided to minimize weight loss as long as the patient consents before the dying phase. When the end of life is very close, only minimal amounts of food and water may be used to reduce thirst and hunger [9]. ASPEN also states that the palliative use of nutrition support therapy in terminally ill cancer patients is rarely indicated [60].

Oral Nutritional Supplements

There are three ways of providing nutritional support: (1) through dietary advice and counseling or oral supplementation, (2) through enteral (tube feeding via a direct gastric or jejunal route), or (3) parenteral nutrition when oral and enteral routes are, for any reason, unavailable [31].

Oral nutritional supplements (ONS) are the commonly available and less invasive way for supporting cancer patients when the primary cause of weight loss is anorexia. The major indication of oral nutritional supplements is mildly malnourished patients, or patients who are in good condition but candidates for a toxic anticancer therapy that has a significant risk of causing major nausea, vomiting, or upper gastrointestinal mucositis. The patients should be able to swallow and their intestines must be functioning [31].

ONS or tube feeding was shown to significantly reduce weight loss compared to normal food in some studies [9]. As a consequence, quality of life could be maintained [96], interruptions of treatment could be prevented [97], and the frequency of hospital admissions could be reduced [93, 97] by ONS.

Immunonutrition

Gastrointestinal cancer surgery is associated with defective immune function and postoperative mortality and morbidity, particularly due to infections [98]. Immunonutrition formulae—containing high-protein and high-energy mixtures of specific nutrients including glutamine; arginine; polyunsaturated fatty acids (omega-3); nucleotides; taurine; vitamins A, E and C; beta-carotene; and trace elements such as zinc and selenium—stimulate host immunity, improve the control of inflammatory response, and increase protein synthesis after major surgery [98]. Studies demonstrated that perioperative immunonutrition is beneficial and associated with a low rate of infectious complications, length of hospital stay, and low cost compared to a standard isocaloric, isoenergy nutritional formulae [99, 100].

Summary of grade A recommendations of ESPEN [101] and ASPEN [102] about immunonutrition is as follows:

- Enteral immunonutrition both oral or through a tube for 5–7 days preoperatively is recommended in all, malnourished and nonmalnourished, patients undergoing gastrointestinal cancer surgery.
- Continue immunonutrition postoperatively in patients who were malnourished preoperatively: (1) for 5–7 days in the absence of complications or (2) until oral feeding has been restored, providing at least 60% of nutritional requirements.
- Use a combination of immunonutrition and physical activity to be more effective, to increase muscle blood flow, increase protein assimilation, and reduce inflammatory state.

Immunonutrition is contraindicated in patients with sepsis and concomitant hemodynamic instability [98].

nutritional support, enteral nutrition is generally seen as superior to parenteral nutrition in a patient with a functioning intestine. ESPEN Guidelines on Enteral Nutrition in Oncology indicate the following:

- Nutritional therapy should be started if under-nutrition already exists or if it is anticipated that the patient will be unable to eat for more than 7 days. EN should also be started if an inadequate food intake (<60% of estimated energy expenditure) is anticipated for more than 10 days [9].

Compelling data in the literature supports the use of enteral nutrition rather than parenteral nutrition with bowel rest in patients with gastrointestinal malignancy. Interest in the enteral route continues to grow, owing to the fact that enteral nutrition is usually less expensive, is nutritionally complete, and has a more physiological administration than intravenous feeding [103]. In patients with cancer, EN may be helpful to maintain and even improve nutritional status. The ESPEN guideline states the following:

- In patients who are losing weight due to insufficient nutritional intake, EN should be provided to improve or maintain nutritional status. This may also contribute to the maintenance of quality of life [9].

As a general rule, parenteral nutrition should be reserved for patients with severe pre-existing malnutrition admitted to the intensive care unit (ICU), and in patients with contraindications to enteral support [104, 105]. This is based on the well-known complications associated with parenteral nutrition administration, both in the long and short term.

A study of 154 esophagus cancer patients compared outcomes in patients receiving parenteral support following thoracic esophagectomy operation versus those receiving enteral nutrition. The enteral group had significantly fewer life-threatening complications and shorter hospital stays than the parenteral group [106].

The role of parenteral support in gastrointestinal cancer patients was investigated in several studies. A systematic review of the literature by the American Gastroenterological Association (AGA) examined randomized trials of parenteral nutritional support in cancer patients and showed that parenteral nutrition did not significantly improve mortality. There was a statistically significant 40% increase in the total complications rate and infectious complications were significantly increased [92, 107]. On the other hand, some studies evaluating early institution of parenteral nutritional support in malnourished patients receiving palliative anticancer treatment concluded that body weight was maintained, and quality of life and survival were significantly improved by the addition of parenteral nutrition to oral enteral nutritional supplementation [92, 108, 109].

Gastrostomy Tubes

Patients who have unresectable or widely metastatic disease, but either desire or require enteral access for feeding or decompression, are good candidates for percutaneous endoscopic gastrostomy (PEG) placement. The lower complication rate and ease of placement make this procedure more valuable [104].

In operable patients with esophagus cancer, PEGs are sometimes avoided because of the risk of injuring the gastroepiploic artery, thus rendering the stomach unusable as a replacement conduit for the esophagus. However, PEG placement is generally a safe procedure in the setting of esophageal cancer, and it does not compromise the stomach or esophagogastric anastomosis [110].

Jejunosotomy (J) tubes are an additional option for enteral access. Existing gastrostomy tubes can be converted to jejunostomy tubes with low morbidity. Placement of a J tube avoids potential injury to the stomach. J tubes can be placed using either an open or a laparoscopic technique. J tubes can also be placed via a percutaneous endoscopic technique [111].

Refeeding Syndrome

During prolonged starvation, fatty acids become the major source of energy at the cellular level, instead of glucose. For this reason, foods with high glucose content may cause some problems in cell functions and integrity, known as refeeding syndrome. In a patient who has been malnourished for days to weeks, if nutritional support is started the patient should be watched carefully for refeeding syndrome, which may cause potentially life-threatening metabolic derangements [112]. Therefore, in such patients, nutritional support should not be very aggressive at the first few days and glucose content should be increased gradually. Although the risk is higher with parenteral feeding, it should be kept in mind that enteral and even oral nutrition are not completely safe with regard to the refeeding syndrome.

Nutritional Support in the Perioperative Period

It is well established that perioperative malnutrition is associated with poor postoperative outcomes in patients undergo-

ing major surgery [113, 114]. Moreover, surgical procedures especially for abdominal cancer may directly affect the nutritional status of patients postoperatively and therefore nutritional evaluation should be performed in all patients going to surgery for their gastrointestinal cancer. Although multiple studies have failed to demonstrate a survival benefit from perioperative nutrition support in patients undergoing major cancer surgery [115–117], others have documented fewer operative complications, and a shorter length of hospital stay in malnourished patients who receive nutritional support [118, 119]. ASPEN does not advise routine nutrition support therapy in patients undergoing major cancer operations and states the following:

- Perioperative nutrition support therapy may be beneficial in moderately or severely malnourished patients if administered for 7–14 days preoperatively, but the potential benefits of nutrition support must be weighed against the potential risks of the nutrition support therapy itself and of delaying the operation [60]. (Grade: A).

ESPEN recommendations about perioperative period of cancer patients are similar:

- Patients with severe nutritional risk benefit from nutritional support for 10–14 days prior to major surgery even if surgery has to be delayed (A). Whenever feasible, the enteral route should be preferred [9](A).
- In all cancer patients undergoing major abdominal surgery, preoperative EN preferably with immune modulating substrates (arginine, x-3 fatty acids and nucleotides) is recommended for 5–7 days independent of their nutritional status [9] (A).

Malnourished patients undergoing major surgery for GI malignancies may have fewer complications when postoperative feeding is accomplished by the enteral, rather than parenteral, route, although the data are conflicting. Comparisons of PN to EN also indicate few differences in morbidity or mortality between the modalities. However, EN is favored to preserve gut integrity and immune markers [60, 103, 120–123] in patients with GI tumor surgery. In another study, early postoperative enteral nutrition in patients with upper gastrointestinal cancer undergoing curative resection results in an improvement in protein kinetics, net balance, and amino acid flux across peripheral tissue compared with intravenous nutrition [124].

There are some studies that raise questions about the magnitude of the benefit from postoperative feeding. In one such report, postoperative enteral nutrition was associated with a significantly higher frequency of delayed gastric emptying and a longer duration of nasogastric tube decompression and hospital stay, but no improvement in postoperative complications in patients undergoing a Whipple procedure for pancreatic cancer [125].

Parenteral nutrition decreases postoperative complications when administered to patients undergoing surgery for cancer, but does not appear to provide a survival benefit, with the possible exception of those who have intestinal failure. Furthermore, there are risks (mostly infectious) associated with its use [126]. Consequently, perioperative enteral nutrition appears to be more beneficial than parenteral nutrition in the reduction of complications and postoperative hospital stay. Enteral nutrition should be used as postoperative nutritional support for malnourished patients with gastrointestinal cancer, provided that there are no contraindications for enteral nutrition [103].

Nutritional Support During Radiotherapy

Although routine use of tube feeding during radiotherapy is not recommended, there is some evidence that tube feeding is beneficial in malnourished dysphagic cancer patients undergoing radiotherapy alone or combined with chemotherapy. Nutritional status can be better preserved and compliance with oncological therapy improved with correct enteral nutrition support [31]. Indications for parenteral nutrition in patients on radiotherapy do not differ from general indications of parenteral nutrition. But in severe mucositis, especially involving the esophagus in patients undergoing chemoradiotherapy, it may be difficult to use the oral route and place a nasogastric tube. In these patients, a short period of parenteral support may be a choice.

ESPEN recommendations on indication for EN during radiotherapy or combined radiochemotherapy are as follows [9]:

- Use intensive dietary counseling and ONS to increase dietary intake (A) and to prevent therapy-associated weight loss and interruption of radiation therapy in patients undergoing radiotherapy of gastrointestinal or head and neck areas (A). If an obstructing head and neck or esophageal cancer interferes with swallowing, EN should be delivered by tube (C).
- TF is also suggested if severe local mucositis is expected, which might interfere with swallowing; e.g., in intensive radiotherapy or in combined modality radiochemotherapy regimens including radiation of throat or esophagus (C).
- TF can either be delivered via the transnasal or percutaneous routes. Because of radiation-induced oral and esophageal mucositis, a PEG may be preferred (C).
- Routine EN is not indicated during radiation therapy of other body regions (C).

Nutritional Support in Incurable and Terminal Patients

Common symptoms of terminal cancer patients—such as nausea, vomiting, loss of appetite, dysphagia, weakness, or gastrointestinal tract obstruction—cause reduced oral intake and insufficient intake of nutrients and fluids before death. Clinical trials failed to demonstrate a positive effect of nutritional supply during this period in reversing weight loss, improving quality of life, or prolonging survival; therefore, most of the guidelines recommend against routine administration of parenteral nutrition in patients with advanced cancer [6, 60, 127]. But, it should be considered that total macronutrient deprivation in ill subjects is associated with substantial mortality within a few weeks. Hence, cancer patients who are unable to eat and who are going to die early from pure starvation rather than from tumor progression can benefit from nutritional support [9].

Home parenteral nutritional support may be considered in patients with malabsorption from advanced cancer or with a malignant bowel obstruction who might otherwise have a prognosis that is measured in months, after extensive deliberation among the healthcare staff, the patient, and family members [126, 128]. However, whether an aphagic, (sub) obstructed incurable cancer patient should be supported through is an extremely controversial topic. This is because, although patients with benign intestinal failure may survive several years with home parenteral nutrition, incurable cancer patients always die after weeks or months despite home parenteral nutrition. Additionally, if possible, long-term nutritional support may be provided enterally at home, usually through a gastrostomy [31].

ESPEN recommends the following:

- EN should be provided in order to minimize weight loss, as long as the patient consents and the dying phase has not started (C). When the end of life is very close, most patients require only minimal amounts of food and little water to reduce thirst and hunger (B). Small amounts of fluid may also help to avoid states of confusion induced by dehydration (B). Subcutaneously infused fluids in the hospital or at home may be helpful and also provide a vehicle for the administration of drugs (C) [9].

Conclusion

In conclusion, cancer-associated malnutrition or cachexia—due to reduced food intake and metabolic derangements—is very prevalent in GI cancer patients. Malnutrition affects all aspects of oncology treatment including toxicity, performance status, quality of life, treatment response, and overall survival. However, combined with surgery, chemotherapy, or radiotherapy, nutritional support can improve tolerance of treatment, quality of life, and long-term outcomes in patients with gastrointestinal cancer. An aggressive multidisciplinary approach should be utilized with nutrition support remaining a cornerstone in the management of these patients.

References

1. Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clin Nutr. 2012;31(3):345–50.
2. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern cooperative oncology group. Am J Med. 1980;69(4):491–7.
3. Bosaeus I, Daneryd P, Svanberg E, Lundholm K. Dietary intake and resting energy expenditure in relation to weight loss in unselected cancer patients. Int J Cancer. 2001;93(3):380–3.
4. Martin L, Jia C, Rouvelas I, Lagergren P. Risk factors for malnutrition after oesophageal and cardia cancer surgery. Br J Surg. 2008;95(11):1362–8.
5. Garabige V, Giraud P, De Rycke Y, Girod A, Jouffroy T, Jaulerry C, et al. Impact of nutrition management in patients with head and neck cancers treated with irradiation: is the nutritional intervention useful? Cancer Radiother. 2007;11(3):111–6.
6. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M, et al. ESPEN guidelines on parenteral nutrition: non-surgical oncology. Clin Nutr. 2009;28(4):445–54.
7. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489–95.
8. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer. 1998;34(4):503–9.
9. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN guidelines on enteral nutrition: non-surgical oncology. Clin Nutr. 2006;25(2):245–59.
10. Sun L, Quan XQ, Yu S. An epidemiological survey of cachexia in advanced cancer patients and analysis on its diagnostic and treatment status. Nutr Cancer. 2015;67(7):1056–62.
11. Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. J Pain Symptom Manag. 2007;34(1):94–104.
12. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European school of oncology task force. Ann Oncol. 2014;25(8):1492–9.
13. Muscaritoli M, Molfino A, Lucia S, Rossi Fanelli F. Cachexia: a preventable comorbidity of cancer. A T.A.R.G.E.T. approach. Crit Rev Oncol Hematol. 2015;94(2):251–9.
14. Rasmussen HH, Holst M, Kondrup J. Measuring nutritional risk in hospitals. Clin Epidemiol. 2010;2:209–16.
15. Barbera L, Seow H, Howell D, Sutradhar R, Earle C, Liu Y, et al. Symptom burden and performance status in a population-based cohort of ambulatory cancer patients. Cancer. 2010;116(24):5767–76.
16. Vigano AL, di Tomasso J, Kilgour RD, Trutschnigg B, Lucar E, Morais JA, et al. The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. J Acad Nutr Diet. 2014;114(7):1088–98.

17. Naboush A, Hamdy O. Measuring visceral and hepatic fat in clinical practice and clinical research. Endocr Pract. 2013;19(4):587–9.
18. Dehghan M, Merchant AT. Is bioelectrical impedance accurate for use in large epidemiological studies? Nutr J. 2008;7:26.
19. Sandri M. Protein breakdown in cancer cachexia. Semin Cell Dev Biol. 2015;54:11–9.
20. Penna F, Costamagna D, Pin F, Camperi A, Fanzani A, Chiarpotto EM, et al. Autophagic degradation contributes to muscle wasting in cancer cachexia. Am J Pathol. 2013;182(4):1367–78.
21. Cariuk P, Lorite MJ, Todorov PT, Field WN, Wigmore SJ, Tisdale MJ. Induction of cachexia in mice by a product isolated from the urine of cachectic cancer patients. Br J Cancer. 1997;76(5):606–13.
22. Eley HL, Tisdale MJ. Skeletal muscle atrophy, a link between depression of protein synthesis and increase in degradation. J Biol Chem. 2007;282(10):7087–97.
23. Chen JL, Walton KL, Winbanks CE, Murphy KT, Thomson RE, Makanji Y, et al. Elevated expression of activins promotes muscle wasting and cachexia. FASEB J. 2014;28(4):1711–23.
24. Gallot YS, Durieux AC, Castells J, Desgeorges MM, Vernus B, Plantureux L, et al. Myostatin gene inactivation prevents skeletal muscle wasting in cancer. Cancer Res. 2014;74(24):7344–56.
25. Mendes MC, Pimentel GD, Costa FO, Carvalheira JB. Molecular and neuroendocrine mechanisms of cancer cachexia. J Endocrinol. 2015;226(3):R29–43.
26. Bing C, Bao Y, Jenkins J, Sanders P, Manieri M, Cinti S, et al. Zinc-alpha2-glycoprotein, a lipid mobilizing factor, is expressed in adipocytes and is up-regulated in mice with cancer cachexia. Proc Natl Acad Sci U S A. 2004;101(8):2500–5.
27. Esposito A, Criscitiello C, Gelao L, Pravettoni G, Locatelli M, Minchella I, et al. Mechanisms of anorexia-cachexia syndrome and rational for treatment with selective ghrelin receptor agonist. Cancer Treat Rev. 2015;41(9):793–7.
28. Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE, et al. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature. 2014;513(7516):100–4.
29. Tsoli M, Moore M, Burg D, Painter A, Taylor R, Lockie SH, et al. Activation of thermogenesis in brown adipose tissue and dysregulated lipid metabolism associated with cancer cachexia in mice. Cancer Res. 2012;72(17):4372–82.
30. Acunzo M, Croce CM. Microrna in cancer and cachexia–a mini-review. J Infect Dis. 2015;212(Suppl 1):S74–7.
31. Bozzetti F. Nutritional support of the oncology patient. Crit Rev Oncol Hematol. 2013;87(2):172–200.
32. Riechelmann RP, Burman D, Tannock IF, Rodin G, Zimmermann C. Phase ii trial of mirtazapine for cancer-related cachexia and anorexia. Am J Hosp Palliat Care. 2010;27(2):106–10.
33. White JP, Puppa MJ, Sato S, Gao S, Price RL, Baynes JW, et al. IL-6 regulation on skeletal muscle mitochondrial remodeling during cancer cachexia in the ApcMin/+ mouse. Skelet Muscle. 2012;2:14.
34. Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment–a systematic review. Crit Rev Oncol Hematol. 2013;88(3):573–93.
35. Maddocks M, Jones LW, Wilcock A. Immunological and hormonal effects of exercise: implications for cancer cachexia. Curr Opin Support Palliat Care. 2013;7(4):376–82.
36. Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, Gonzalvez Perales JL, Bort-Marti S. Megestrol acetate for treatment of anorexia-cachexia syndrome. Cochrane Database Syst Rev. 2013;3:CD004310.
37. Evans WJ. Editorial: Megestrol acetate use for weight gain should be carefully considered. J Clin Endocrinol Metab. 2007;92(2):420–1.
38. Paulsen O, Klepstad P, Rosland JH, Aass N, Albert E, Fayers P, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. J Clin Oncol. 2014;32(29):3221–8.
39. Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol. 2013;31(25):3076–82.
40. Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a north central cancer treatment group study. J Clin Oncol. 2002;20(2):567–73.
41. Strasser F, Luftner D, Possinger K, Ernst G, Ruhstaller T, Meissner W, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the cannabis-in-cachexia-study-group. J Clin Oncol. 2006;24(21):3394–400.
42. Brisbois TD, de Kock IH, Watanabe SM, Mirhosseini M, Lamoureux DC, Chasen M, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann Oncol. 2011;22(9):2086–93.
43. Ries A, Trottenberg P, Elsner F, Stiel S, Haugen D, Kaasa S, et al. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project. Palliat Med. 2012;26(4):294–304.
44. Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, Mazurak VC. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. Cancer. 2011;117(8):1775–82.
45. Lambert CP, Sullivan DH, Freeling SA, Lindquist DM, Evans WJ. Effects of testosterone replacement and/or resistance exercise on the composition of megestrol acetate stimulated weight gain in elderly men: a randomized controlled trial. J Clin Endocrinol Metab. 2002;87(5):2100–6.
46. Dobs AS, Boccia RV, Croot CC, Gabrail NY, Dalton JT, Hancock ML, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. Lancet Oncol. 2013;14(4):335–45.
47. Temel J, Bondarde S, Jain M, et al. Efficacy and safety results from phase 2 study of anamorelin HCL, aghrelin receptor agonsit, in NSCLC patients. J Cachexia Sarcopenia Muscle. 2013;4:295–343.
48. Garcia JM, Boccia RV, Graham CD, Yan Y, Duus EM, Allen S, et al. Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. Lancet Oncol. 2015;16(1):108–16.
49. Temel JS, Currow DC, Fearon K, et al. Phase 3 trials of anamorelin in patients with advanced non-small lung cancer and cachexia (ROMANA 1 and 2). Lancet Oncol. 2016;17(4):519–31.
50. Currow DC, Temel JS, Fearon K, et al. A safety extension study of anamorelin in advanced non-small cell lung cancer patients with cachexia: ROMANA 3. Ann Oncol. 2017;28(8):1949–56.
51. Senesse P, Assenat E, Schneider S, Chargari C, Magné N, Azria D, et al. Nutritional support during oncologic treatment of patients with gastrointestinal cancer: who could benefit? Cancer Treat Rev. 2008;34(6):568–75.
52. Leuenberger M, Kurmann S, Stanga Z. Nutritional screening tools in daily clinical practice: the focus on cancer. Support Care Cancer. 2010;18(Suppl 2):S17–27.
53. Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of

nutrition support in patients with cancer. JPEN J Parenter Enteral Nutr. 2014;38(2):196–204.
54. Gupta D, Vashi PG, Lammersfeld CA, Braun DP. Role of nutritional status in predicting the length of stay in cancer: a systematic review of the epidemiological literature. Ann Nutr Metab. 2011;59(2–4):96–106.
55. Bauer J, Capra S, Ferguson M. Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr. 2002;56(8):779–85.
56. Afaneh C, Gerszberg D, Slattery E, Seres DS, Chabot JA, Kluger MD. Pancreatic cancer surgery and nutrition management: a review of the current literature. Hepatobiliary Surg Nutr. 2015;4(1):59–71.
57. Demling RH. Nutrition, anabolism, and the wound healing process: an overview. Eplasty. 2009;9:e9.
58. Schneider SM, Veyres P, Pivot X, Soummer AM, Jambou P, Filippi J, et al. Malnutrition is an independent factor associated with nosocomial infections. Br J Nutr. 2004;92(1):105–11.
59. de Luis DA, Izaola O, Cuellar L, Terroba MC, Cabezas G, Rojo S, et al. Nutritional assessment: predictive variables at hospital admission related with length of stay. Ann Nutr Metab. 2006;50(4):394–8.
60. August DA, Huhmann MB, Directors ASfPaENASPENBo. A.S.P.E.N. Clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. JPEN J Parenter Enteral Nutr. 2009;33(5):472–500.
61. Mueller C, Compher C, Ellen DM, Directors ASfPaENASPENBo. A.S.P.E.N. Clinical guidelines: nutrition screening, assessment, and intervention in adults. JPEN J Parenter Enteral Nutr. 2011;35(1):16–24.
62. Davis CJ, Sowa D, Keim KS, Kinnare K, Peterson S. The use of prealbumin and C-reactive protein for monitoring nutrition support in adult patients receiving enteral nutrition in an urban medical center. JPEN J Parenter Enteral Nutr. 2012;36(2):197–204.
63. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Group AHEW. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321–36.
64. Elia M. Screening for malnutrition: a multidsiplinary responsibility. Development and use of malnutrition universal screening tool for adults. BAPEN, 2003.
65. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? 1987. Classical article. Nutr Hosp. 2008;23(4):400–7.
66. Guigoz Y. The mini nutritional assessment (MNA) review of the literature–what does it tell us? J Nutr Health Aging. 2006;10(6):466–85.. discussion 485–67
67. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. Educational and Clinical Practice Committee ErSoPaENE. ESPEN guidelines for nutrition screening 2002. Clin Nutr. 2003;22(4):415–21.
68. Read JA, Crockett N, Volker DH, MacLennan P, Choy ST, Beale P, et al. Nutritional assessment in cancer: comparing the mini-nutritional assessment (MNA) with the scored patient-generated subjective global assessment (PGSGA). Nutr Cancer. 2005;53(1):51–6.
69. Huhmann MB, August DA. Review of American society for parenteral and enteral nutrition (ASPEN) clinical guidelines for nutrition support in cancer patients: nutrition screening and assessment. Nutr Clin Pract. 2008;23(2):182–8.
70. Huhmann MB, August DA. Perioperative nutrition support in cancer patients. Nutr Clin Pract. 2012;27(5):586–92.
71. Omran ML, Morley JE. Assessment of protein energy malnutrition in older persons, part I: history, examination, body composition, and screening tools. Nutrition. 2000;16(1):50–63.
72. Omran ML, Morley JE. Assessment of protein energy malnutrition in older persons, part II: laboratory evaluation. Nutrition. 2000;16(2):131–40.
73. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr. 2004;23(6):1430–53.
74. Kyle UG, Genton L, Pichard C. Body composition: what's new? Curr Opin Clin Nutr Metab Care. 2002;5(4):427–33.
75. Prado CM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res. 2007;13(11):3264–8.
76. Kyle UG, Soundar EP, Genton L, Pichard C. Can phase angle determined by bioelectrical impedance analysis assess nutritional risk? A comparison between healthy and hospitalized subjects. Clin Nutr. 2012;31(6):875–81.
77. Kyle UG, Genton L, Pichard C. Low phase angle determined by bioelectrical impedance analysis is associated with malnutrition and nutritional risk at hospital admission. Clin Nutr. 2013;32(2):294–9.
78. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.
79. Dalal S, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, et al. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. J Pain Symptom Manag. 2012;44(2):181–91.
80. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing. 2010;39(4):412–23.
81. Visser M, Schaap LA. Consequences of sarcopenia. Clin Geriatr Med. 2011;27(3):387–99.
82. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg. 2012;99(4):550–7.
83. Levolger S, van Vugt JL, de Bruin RW, IJzermans JN. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. Br J Surg. 2015;102(12):1448–58.
84. Fruchtenicht AV, Poziomyck AK, Kabke GB, Loss SH, Antoniazzi JL, Steemburgo T, et al. Nutritional risk assessment in critically ill cancer patients: systematic review. Rev Bras Ter Intensiva. 2015;27(3):274–83.
85. Dempsey DT, Feurer ID, Knox LS, Crosby LO, Buzby GP, Mullen JL. Energy expenditure in malnourished gastrointestinal cancer patients. Cancer. 1984;53(6):1265–73.
86. Hansell DT, Davies JW, Burns HJ. Effects of hepatic metastases on resting energy expenditure in patients with colorectal cancer. Br J Surg. 1986;73(8):659–62.
87. Hansell DT, Davies JW, Burns HJ. The effects on resting energy expenditure of different tumor types. Cancer. 1986;58(8):1739–44.
88. Fredrix EW, Soeters PB, Wouters EF, Deerenberg IM, von Meyenfeldt MF, Saris WH. Effect of different tumor types on resting energy expenditure. Cancer Res. 1991;51(22):6138–41.
89. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996–1002.

90. Barrera R. Nutritional support in cancer patients. JPEN J Parenter Enteral Nutr. 2002;26(5 Suppl):S63–71.
91. Nitenberg G, Raynard B. Nutritional support of the cancer patient: issues and dilemmas. Crit Rev Oncol Hematol. 2000;34(3):137–68.
92. Jatoi A, Loprinzi CL. Current management of cancer-associated anorexia and weight loss. Oncology (Williston Park). 2001;15(4):497–502, 508; discussion 508–410.
93. Bozzetti F, Cozzaglio L, Gavazzi C, Bidoli P, Bonfanti G, Montalto F, et al. Nutritional support in patients with cancer of the esophagus: impact on nutritional status, patient compliance to therapy, and survival. Tumori. 1998;84(6):681–6.
94. Jatoi A, Rowland K, Loprinzi CL, Sloan JA, Dakhil SR, MacDonald N, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a north central cancer treatment group and national cancer institute of Canada collaborative effort. J Clin Oncol. 2004;22(12):2469–76.
95. Elia M, Van Bokhorst-de van der Schueren MA, Garvey J, Goedhart A, Lundholm K, Nitenberg G, et al. Enteral (oral or tube administration) nutritional support and eicosapentaenoic acid in patients with cancer: a systematic review. Int J Oncol. 2006;28(1):5–23.
96. Thiel HJ, Fietkau R, Sauer R. Malnutrition and the role of nutritional support for radiation therapy patients. Recent Results Cancer Res. 1988;108:205–26.
97. Daly JM, Weintraub FN, Shou J, Rosato EF, Lucia M. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. Ann Surg. 1995;221(4):327–38.
98. Mariette C. Immunonutrition. J Visc Surg. 2015;152(Suppl 1):S14–7.
99. Gianotti L, Braga M, Fortis C, Soldini L, Vignali A, Colombo S, et al. A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. JPEN J Parenter Enteral Nutr. 1999;23(6):314–20.
100. Gianotti L, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. Gastroenterology. 2002;122(7):1763–70.
101. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN guidelines on enteral nutrition: surgery including organ transplantation. Clin Nutr. 2006;25(2):224–44.
102. McClave SA, Kozar R, Martindale RG, Heyland DK, Braga M, Carli F, et al. Summary points and consensus recommendations from the North American Surgical Nutrition Summit. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):99S–105S.
103. Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial. Lancet. 2001;358(9292):1487–92.
104. Miller KR, Bozeman MC. Nutritional therapy in esophageal cancer. Curr Gastroenterol Rep. 2012;14(4):356–66.
105. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–316.
106. Fujita T, Daiko H, Nishimura M. Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer. Eur Surg Res. 2012;48(2):79–84.
107. Koretz RL, Lipman TO, Klein S, Association AG. Aga technical review on parenteral nutrition. Gastroenterology. 2001;121(4):970–1001.
108. Shang E, Weiss C, Post S, Kaehler G. The influence of early supplementation of parenteral nutrition on quality of life and body composition in patients with advanced cancer. JPEN J Parenter Enteral Nutr. 2006;30(3):222–30.
109. Hasenberg T, Essenbreis M, Herold A, Post S, Shang E. Early supplementation of parenteral nutrition is capable of improving quality of life, chemotherapy-related toxicity and body composition in patients with advanced colorectal carcinoma undergoing palliative treatment: results from a prospective, randomized clinical trial. Color Dis. 2010;12(10 Online):e190–9.
110. Margolis M, Alexander P, Trachiotis GD, Gharagozloo F, Lipman T. Percutaneous endoscopic gastrostomy before multimodality therapy in patients with esophageal cancer. Ann Thorac Surg. 2003;76(5):1694–7.. discussion 1697–8
111. Blumenstein I, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. World J Gastroenterol. 2014;20(26):8505–24.
112. Marinella MA. Refeeding syndrome: an important aspect of supportive oncology. J Support Oncol. 2009;7(1):11–6.
113. Studley HO. Percentage of weight loss: a basic indicator of surgical risk in patients with chronic peptic ulcer. 1936. Nutr Hosp. 2001;16(4):141–3.. discussion 140–41
114. Rhoads JE, Alexander CE. Nutritional problems of surgical patients. Ann N Y Acad Sci. 1955;63(2):268–75.
115. Brennan MF, Pisters PW, Posner M, Quesada O, Shike M. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. Ann Surg. 1994;220(4):436–41.. discussion 441–34
116. Detsky AS, Baker JP, O'Rourke K, Goel V. Perioperative parenteral nutrition: a meta-analysis. Ann Intern Med. 1987;107(2):195–203.
117. Smith RC, Hartemink RJ, Hollinshead JW, Gillett DJ. Fine bore jejunostomy feeding following major abdominal surgery: a controlled randomized clinical trial. Br J Surg. 1985;72(6):458–61.
118. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med. 1994;331(23):1547–52.
119. Bozzetti F, Gavazzi C, Miceli R, Rossi N, Mariani L, Cozzaglio L, et al. Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomized, clinical trial. JPEN J Parenter Enteral Nutr. 2000;24(1):7–14.
120. Sand J, Luostarinen M, Matikainen M. Enteral or parenteral feeding after total gastrectomy: prospective randomised pilot study. Eur J Surg. 1997;163(10):761–6.
121. Aiko S, Yoshizumi Y, Sugiura Y, Matsuyama T, Naito Y, Matsuzaki J, et al. Beneficial effects of immediate enteral nutrition after esophageal cancer surgery. Surg Today. 2001;31(11):971–8.
122. Papapietro K, Díaz E, Csendes A, Díaz JC, Burdiles P, Maluenda F, et al. Early enteral nutrition in cancer patients subjected to a total gastrectomy. Rev Med Chil. 2002;130(10):1125–30.
123. Aiko S, Yoshizumi Y, Matsuyama T, Sugiura Y, Maehara T. Influences of thoracic duct blockage on early enteral nutrition for patients who underwent esophageal cancer surgery. Jpn J Thorac Cardiovasc Surg. 2003;51(7):263–71.
124. Harrison LE, Hochwald SN, Heslin MJ, Berman R, Burt M, Brennan MF. Early postoperative enteral nutrition improves peripheral protein kinetics in upper gastrointestinal cancer patients undergoing complete resection: a randomized trial. JPEN J Parenter Enteral Nutr. 1997;21(4):202–7.

125. Martignoni ME, Friess H, Sell F, Ricken L, Shrikhande S, Kulli C, et al. Enteral nutrition prolongs delayed gastric emptying in patients after Whipple resection. Am J Surg. 2000;180(1):18–23.
126. Hoda D, Jatoi A, Burnes J, Loprinzi C, Kelly D. Should patients with advanced, incurable cancers ever be sent home with total parenteral nutrition? A single institution's 20-year experience. Cancer. 2005;103(4):863–8.
127. Arends J, Zuercher G, Dossett A, Fietkau R, Hug M, Schmid I, et al. Non-surgical oncology – guidelines on parenteral nutrition, chapter 19. Ger Med Sci. 2009;7:Doc09.
128. Brard L, Weitzen S, Strubel-Lagan SL, Swamy N, Gordinier ME, Moore RG, et al. The effect of total parenteral nutrition on the survival of terminally ill ovarian cancer patients. Gynecol Oncol. 2006;103(1):176–80.

Management of Peritoneal Malignancies

23

Richard N. Berri and Jennifer M. Ford

Introduction

Peritoneal malignancies may result in a widespread disease process, peritoneal carcinomatosis (PC), which has significant morbidity and mortality for patients afflicted by this disease. Dissemination into the peritoneum and throughout the abdomen can be due to a primary peritoneal cancer or other primary malignancies that have metastasized, including (but not limited to) colorectal cancer, gastric cancer, pancreatic cancer, appendiceal cancer, ovarian cancer, and mesothelioma. Patients with gastrointestinal (GI) or gynecologic malignancies with peritoneal carcinomatosis may have dismal survival due to a high disease burden within the abdominal cavity [1]. Some studies suggest the average survival for patients with peritoneal carcinomatosis of colorectal origin is 18–48 months, for high-grade appendiceal adenocarcinoma 12–36 months, and for low-grade appendiceal neoplasms >60 months [1].

As the understanding of peritoneal malignancies and peritoneal carcinomatosis evolved, it may now be acceptable to treat this as locoregional disease [2]. Dr. Paul Sugarbaker, a pioneer in the management of peritoneal cancer, was instrumental in this paradigm shift and his emphasis on accurate assessment of the locoregional tumor burden helped develop the current treatment pathways that are followed today. Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) is now the accepted treatment for PC in select patients with acceptable disease burden from particular malignancies and a good functional status (Table 23.1) [3–5]. The ultimate goal of HIPEC is to destroy microscopic disease left behind after optimal CRS. As outlined by the American Society of Peritoneal Surface Malignancies, indications for CRS with HIPEC are as follows: a large volume of noninvasive peritoneal carcinomatosis or sarcomatosis, peritoneal mesothelioma, low-volume peritoneal seeding from invasive cancer, perforated GI cancer, cancer adherent to adjacent organs or structures, GI cancer with positive peritoneal cytology, GI with ovarian involvement, intraoperative tumor spill, or after systemic chemotherapy for recurrent ovarian cancer after a long disease-free interval and for palliation of patients with malignant ascites [6].

Table 23.1 Comparing survival rates with CRS + HIPEC versus chemotherapy (CT) alone

			Mean survival (months)
Author/study	Disease	CRS + HIPEC	CT alone
Netherlands Cancer Institute [3]	Colorectal with peritoneal metastasis or + cytology	22.2	12.6
Elias et al. [4]	Colorectal with peritoneal metastasis	62.7	23.9
Glehen et al. [5]	Colorectal cancer	19.2	–

Patient Selection and Diagnosis

Perhaps the most important factor in this disease entity is patient selection and establishing which patients may benefit from a surgical approach. This can be extremely challenging. Patients who present for evaluation need a comprehensive workup to establish a diagnosis and determine the extent of disease. Ideally, patients should be referred to high-volume centers that have extensive experience in diagnosing and treating peritoneal malignancies. A detailed physical examination and history, including all previous treatments and

R. N. Berri (✉)
Surgical Oncology, Peritoneal Malignancies Program, Department of Surgery, Ascension, St. John Hospital, Grosse Pointe, MI, USA
e-mail: Richard.Berri@ascension.org

J. M. Ford
Department of Surgery, Astria Regional Medical Center and Heart Institute, Yakima, WA, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_23

Table 23.2 The Eastern Cooperative Oncology Group (ECOG) Performance Status categories [7]

Grade	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

when they occurred, should be established during the first evaluation. The two factors that will ultimately have the most substantial impact on the outcome of the patient is the histology of the primary tumor and the overall burden of peritoneal disease.

Optimization of preoperative performance status (PS), activity level, and comorbidities cannot be overemphasized. Often employed is the Eastern Cooperative Oncology Group (ECOG) Performance Status; this scale ranges from 0 to 5 and provides a concise method to assess performance status and activity level of patients (see Table 23.2) [7]. Comorbidities should be well controlled both preoperatively and postoperatively. Previously diagnosed comorbidities are present in 18% of patients undergoing major oncologic resection. These morbidities increase the risk of acute medical complications (odds ratio [OR] 3.7), in-hospital mortality (OR 3.6), hospital costs, postoperative complications (OR 3.9), and increased complication severity (OR 3.6) [8].

The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) calculator is a tool that can assist in preoperative evaluation. A recent study from our institution validated the risk calculator for use in this patient population [9]. The risk calculator is a reasonable tool and is now integrated into our preoperative evaluation.

Any patient who demonstrates a poor PS or uncontrolled comorbidities must be optimized prior to considering surgical resection in such a way that is similar to any patient being evaluated for any complicated GI oncologic resection. Patients benefit from a regimen of physical activity, smoking cessation, and medical and nutritional optimization. Additionally, the procedure, recovery, outcomes, and possible adverse effects must all be explained to the patient so they have a comprehensive understanding and not unrealistic expectations.

Radiographic Imaging

The use of imaging is essential and is in some cases diagnostic of peritoneal carcinomatosis. It is able to reasonably discern those patients that demonstrate hematogenous metastasis outside of the peritoneal cavity and non-resectable liver, lung, or other distant metastasis and are therefore not surgical candidates. However, an important tenant of peritoneal cancer is that *any and all* imaging modalities may most often dramatically underestimate the true volume and burden of peritoneal carcinomatosis. Importantly, this must be kept in mind in the preoperative surgical planning and especially in discussion with the patient to alert them of this possibility of "understaging" with imaging (Fig. 23.1) [10].

Imaging modalities used include computed tomography (CT), magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan, and ultrasound (US). US can identify the presence of ascites and can be used for image-guided biopsy or identification of large intra-abdominal masses [2]. CT scan or, if available, MRI with peritoneal malignancy protocol is the method most often employed. It can discern size (of nodules), location, type of PC, and possible primary sites (Figs. 23.2 and 23.3) [2].

The use of multiplanar CT image reconstruction helps identify lesions that are small (<5 mm) or located in difficult to visualize anatomic positions, such as paracolic gutter or hepatorenal space. Smaller nodules (<5 mm) are better visualized when located on the surface of a larger solid organ, such as the spleen or liver [2]. An extremely valuable fundamental is that the inherent movement of fluid within the abdomen deposits disease first within the right upper quadrant/right subdiaphragmatic peritoneum, followed by the left subphrenic space. In the lower abdomen, the rectovaginal pouch/pouch of Douglas is the initial collection space, followed by deposits around the urinary bladder then the paracolic gutters.

The provisional different types of PC are sclerotic, infiltrative, micronodular/military, and macronodular/nodus. These are often identifiable on CT but much overlap between types exists. Therefore categorization is based on dominant radiographic characteristics. Peritoneal folds appear thickened (diffuse or focal) with sclerotic, jellylike, reticular, reticulonodular, nodular, or large plaques [2].

The sclerotic type often involves the mesentery that appears thickened and retracted [2]. The greater omentum can demonstrate "omental caking," which is a thick heterogeneous neoplastic mixture of micronodular, nodular, or large plaque disease [2]. When calcifications are identified it is often due to the presence of nodular or plaque lesions [2]. These lesions show cyst-like appearances with various levels of attenuation [2].

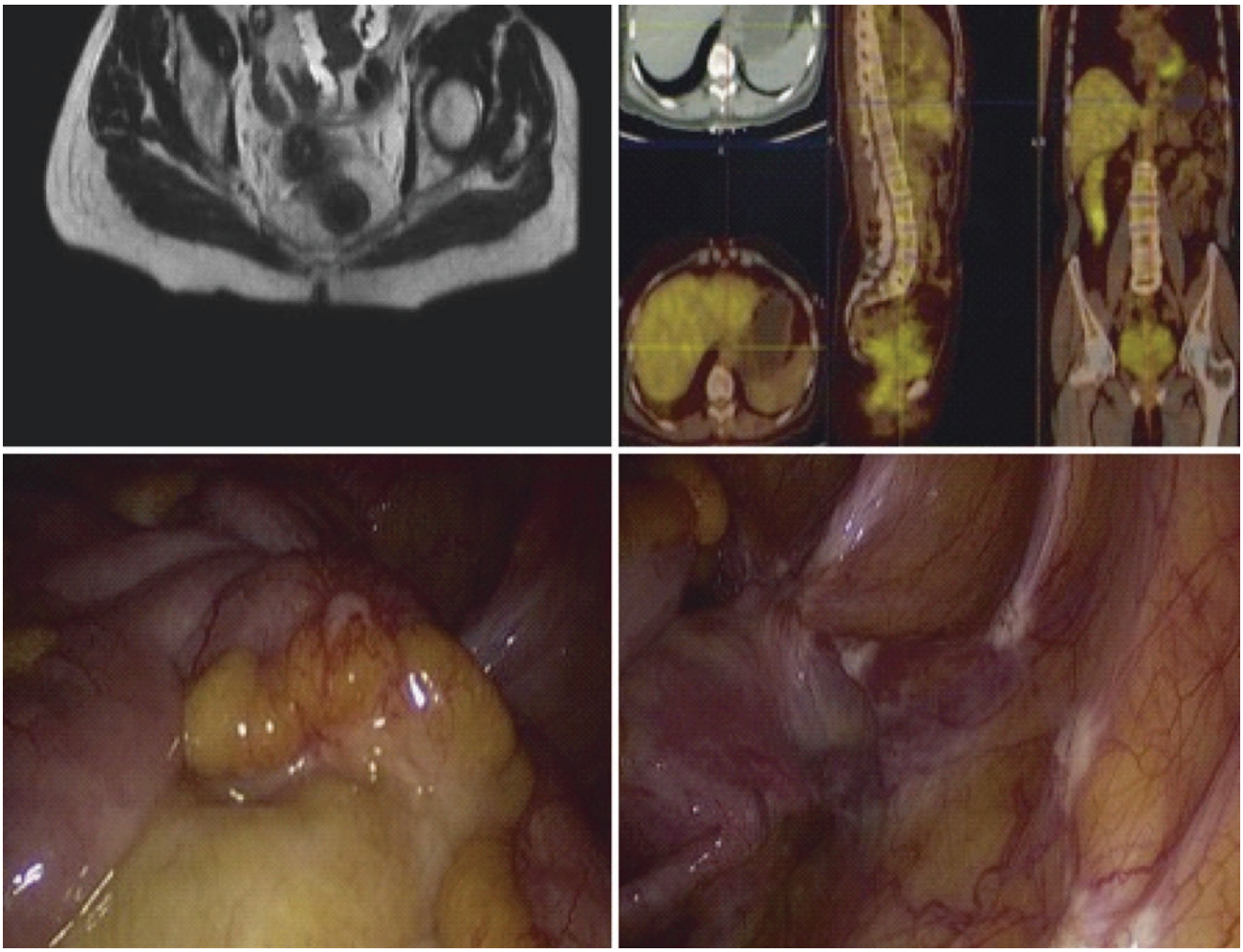


Fig. 23.1 Top left and right: CT, MRI, PET all negative. Bottom (L and R): laparoscopy with gross disease in a patient with colorectal peritoneal carcinomatosis. (Reprinted with permission from Valle et al. [10].)

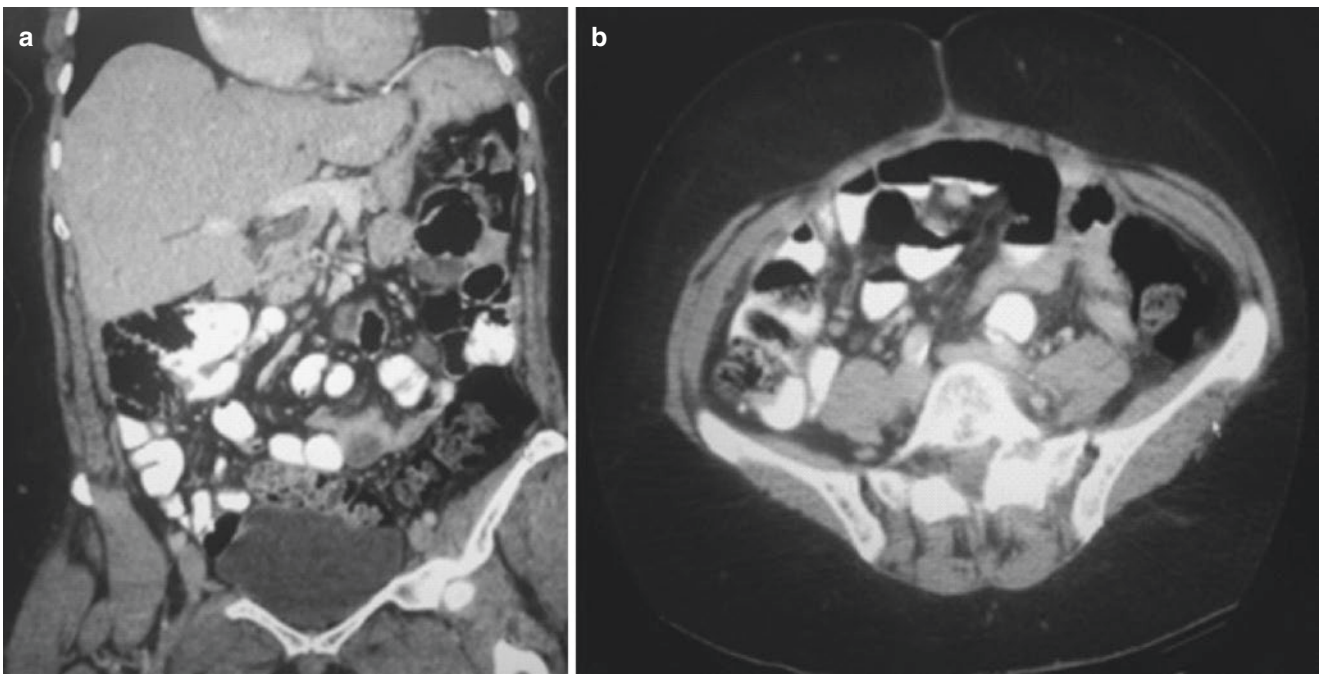


Fig. 23.2 (**a**, **b**) A patient's CT scan that contains minimal mucinous ascites and disease

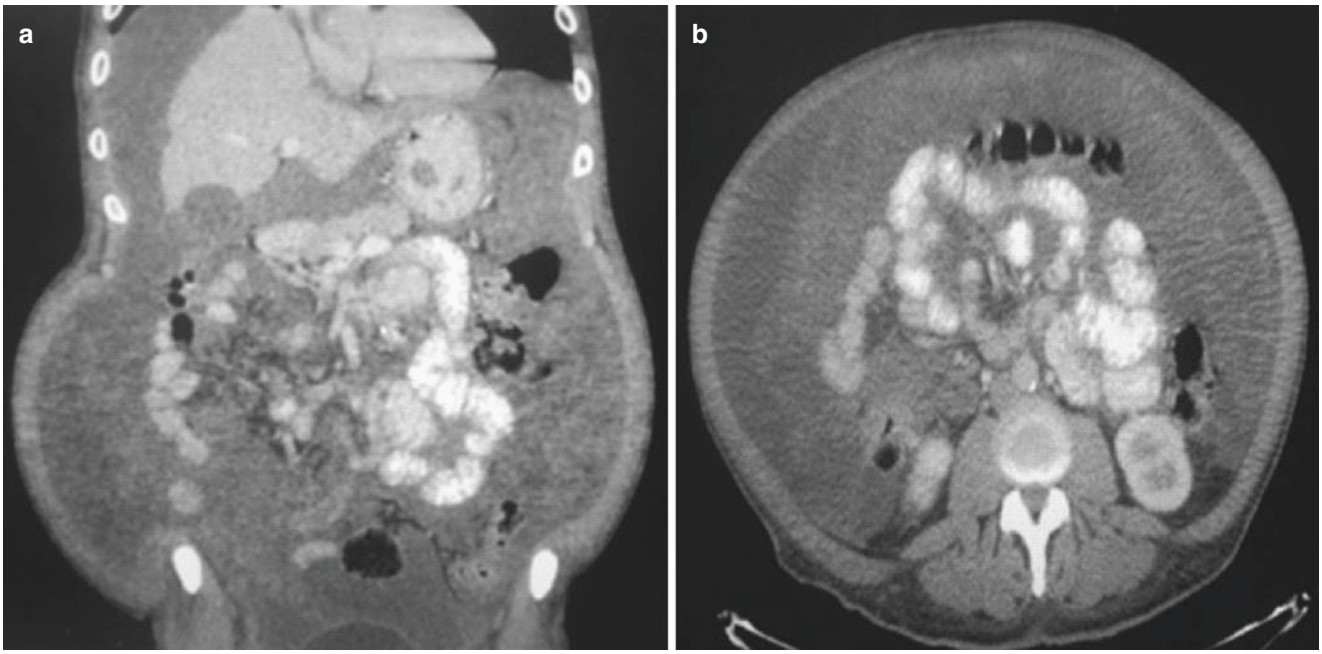


Fig. 23.3 (**a**, **b**) A patient's CT scan that shows a large volume of mucinous ascites and significant disease

Additional findings present on CT include ascites. Ascites of greater than 50 mL (and therefore identifiable on CT) is present in more than 70% of patients [2]. Ascites may be located freely throughout the abdomen or entrapped in different quadrants. Invasive peritoneal nodules can sometimes cause encasement of the large and small bowel on the serosa or mesentery resulting in complete or partial obstruction. Mucinous ascites will irritate the peritoneum causing a fibrotic reaction, which results in thickening of the peritoneal surfaces and may possibly lead to intestinal obstruction [2].

If not already surgically removed, the primary site of the cancer can also be sometimes identified—although a combination of endoscopy and laparoscopy may be necessary. It can be evaluated along with peritoneal spread and intra-abdominal metastases. If no primary lesion is identifiable with imaging, endoscopy, and laparoscopy, a primary peritoneal neoplasm can be considered. Localized PC will be in close proximity to the primary lesion while diffuse is spread to most of the peritoneal surfaces. CT is particularly helpful when the head of the pancreas, porta hepatis, liver, and root of the mesentery are involved with metastatic disease [2]. The accuracy of CT decreases with assessment of small bowel disease and lesions <5 mm [2].

MRI has demonstrated no diagnostic advantage over CT or in prediction of completeness of cytoreduction [2]. However, we recently implemented an MRI with peritoneal protocol that may have advantages in imaging the peritoneum, especially in the surveillance plan of young patients after surgery. Evaluation by PET scan (when used alone), often underestimates disease and may underestimate the disease burden when lesions are <5 mm [11, 12].

Furthermore, the ability of the radiologist to detect peritoneal disease on any imaging study may vary significantly between institutions, thus allowing centers with more experience to accumulate expertise through experience and familiarity with this patient group.

Multidisciplinary Tumor Board

The use of a multidisciplinary tumor board (MDT) provides a comprehensive approach to the patient's complex disease and extensive treatment history. It allows experts from a wide variety of medical and surgical specialties to prospectively review the patient's case and collectively determine the treatment most beneficial for the patient. The use of a multidisciplinary tumor board is now the standard in cancer care. The American College of Surgeons Commission on Cancer Program requires that each institution employ an MDT for case review and treatment decisions to receive proper accreditation [13]. An MDT is an education resource for providers, residents, and medical student; it increases awareness of different specialist's perspectives on the approach to specific cancers [13].

Each patient who presents with PC from a disseminated GI or gynecologic malignancy should be presented at the MDT. The internal structure of each meeting is variable according to institution. Typically, the patient's case is pre-

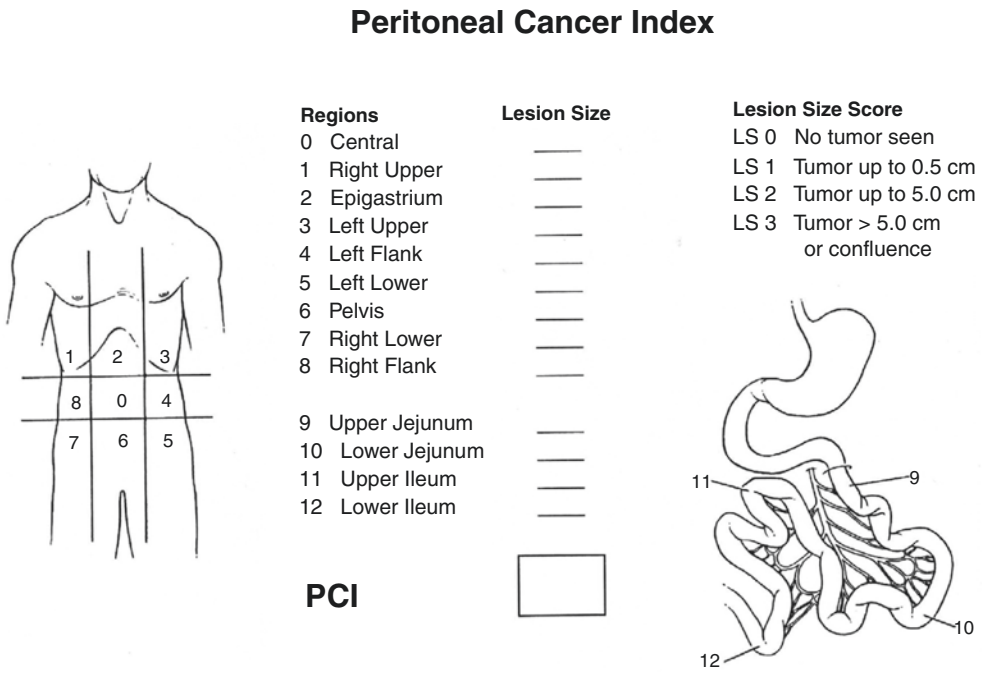


Fig. 23.4 The peritoneal cancer index. (Reprinted with permission from Harmon and Sugarbaker [11]. Under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0))

sented in detail: previous diagnosis, previous treatments (surgical and nonsurgical), reason(s) for presentation at the MDT, current physical exam, performance status, radiographic evidence, pathologic evidence, histology, and other elements of the patient's case are reviewed and discussed. Thus, all participants can contribute to developing a patient-specific treatment plan that could include further diagnostic tests, chemotherapy, radiation therapy, surgery, no intervention, or any combination thereof. It is essential that all cases of peritoneal cancer are routinely presented in GI tumors board meetings before treatment decision.

Resection Guidelines/Operative Indications

In the selection of operative candidates, one may consider the following: age, comorbidities, previous surgeries, previous chemotherapy/radiation, disease-free interval from previous interventions, histology of primary tumor, peritoneal cancer index (PCI), completeness of cytoreductive index (CCR) predicted and the peritoneal surface disease severity score (PSDSS), prior surgery score (PSS), and simplified PCI.

PCI is a tool used to quantify the disease in the abdomen and has been found to be an accurate assessment of survival [11]. It is most accurate when calculated at the time of operation, however preoperative radiographic evaluation shows reasonable sensitivity with high-volume tumors (100%) [2]. However, radiographic PCI decreased in accuracy with small bowel involvement (sensitivity of 8–17%) or lesions <5 mm (sensitivity 11%) [2]. It is a scoring system that divides the abdomen into 13 regions and a lesion size score (LSS) is assigned to each region [11]. Primary lesions or localized recurrences are excluded from the lesion size assessment (Fig. 23.4) [11]. The lesion sizes for all regions are summated and the total score is assigned from 0 to 39.

Anatomic landmarks help divide the regions of the abdomen. The upper transverse plane is located at the lowest part of the costal margin; the lower transverse plane is located at the anterior superior iliac spine (ASIS). The sagittal planes divide into three equal columns. Region 0 is located at the umbilicus, region 1 is located in the right hemidiaphragm, and numbers continue in a clockwise direction [12]. Anatomic structures within each region are defined in Table 23.3 [11].

In particular, patients with colorectal cancer and other invasive cancers should have a thorough evaluation and a documented PCI before committing them to CRS and HIPEC. In 2010, a multicenter French study reported by Elias et al. looked at the role of the PCI in patients with colorectal carcinomatosis treated with surgery and HIPEC [14]. In this study it was shown that as the PCI increased above 20 in patients with CRC and PC, the survival dramatically declined despite having undergone CRS and HIPEC at an experienced center. In fact, in this data, there were no 5-year survivors if the PCI was greater than 20, yet in those patients with a PCI of 1–6, the 5-year survival was over 40% with a median survival of 40 months [14]. At out our center we most often decline patients with PC from CRC and other invasive malignancies for HIPEC if the PCI is greater than 20. However, even if patients with invasive cancer have a PCI less than 20 that is not an absolute indication to proceed

Table 23.3 Anatomic structures located in each abdominal region

Regions	Anatomic structures
0 central	Midline abdominal structures: greater omentum, transverse colon
1 right upper	Superior surface of the right lobe of the liver, undersurface of the right hemidiaphragm, right retro hepatic space
2 epigastrium	Epigastric fat pad, left lobe of liver, lesser omentum, falciform ligament
3 left upper	Undersurface of the left hemidiaphragm, spleen, tail of pancreas, anterior and posterior surfaces of the stomach
4 left flank	Descending colon, left abdominal gutter
5 left lower	Pelvic sidewall lateral to the sigmoid colon, sigmoid colon
6 pelvis	Female internal genitalia with ovaries, tubes and uterus, bladder, pouch of Douglas, rectosigmoid colon
7 right lower	Right pelvic side wall, cecum, appendix
8 right flank	Right abdominal gutter, ascending colon
9 upper jejunum 10 lower jejunum 11 upper ileum 12 lower ileum	

Adapted from Harmon and Sugarbaker [11]. Under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0)

Table 23.4 Peritoneal surface disease severity score

Clinical	PCI	Histology [colonic/*appendiceal*]
No symptoms 0 points	PCI <10 **1 point**	Well differentiated Moderately differentiated/N0 *Low-grade mucinous neoplasm* **1 point**
Mild symptoms 1 point	PCI 10–20 **3 points**	Moderately differentiated/N1 or N2 *Mucinous adenocarcinoma* **3 points**
Severe symptoms 6 points	PCI >20 **7 points**	Every poorly differentiated Every signet ring *High-grade mixed adenocarcinoma and goblet cell carcinoma* **9 points**

Modified from Pelz et al. [12]

with CRS and HIPEC. An example of this is in patients with an unresectable volume of tumor localized in one area, such as the porta hepatis; although the PCI is low, complete cytoreduction may not be possible and these patients generally should not be considered for HIPEC.

A noted exception to the PCI >20 rule is in those patients with low-grade appendiceal mucinous neoplasms (classic pseudomyxoma peritonei) or peritoneal mesothelioma. In those patients a PCI greater than 20 and even close to 39 can be found yet should not serve as a contraindication to cytoreduction and HIPEC because of the favorable long-term prognosis if those patients receive complete cytoreduction and HIPEC.

Arguably, the most important prognostic factor of treatment success is the CCR [2, 11, 12]. Multiple studies have shown improved survival in patients who had undergone complete cytoreduction for appendiceal, colorectal, and gastric cancers [11]. It is a good prognostic indicator for many different histopathologies. We urge that all patients who undergo cytoreduction should have the benefit of a team that can and always aims to achieve a complete cytoreduction. Complete cytoreduction versus incomplete cytoreduction are the main determinants. A CCR of 0 is achieved when there is no peritoneal seeding visualized within the abdomen after cytoreduction [11]. CCR 1 occurs when nodules <2.5 mm persist after CRS [11]. A CCR 2 has residual nodules between 2.5 mm and 2.5 cm, and a CCR 3 indicates nodules >2.5 cm [11]. In order to proceed with HIPEC we advise a CCR of 0 or 1. This is due to the finding that the CCR-1 tumor size (but not CCR-2 and above) is thought to be penetrable by intraperitoneal chemotherapy, thus allowing HIPEC to complete the surgical cytoreduction. Furthermore, Sugarbaker and others have shown that the chance of survival for patients with a CCR 0 from a CRC with PC who underwent HIPEC to be 40% at 5 years, yet 0% survived 5 years when cytoreduction was incomplete (CCR 2 and above) [15].

In experienced centers, for very select patients with incomplete cytoreduction, such as those with refractory malignant ascites, HIPEC may be acceptable even though complete cytoreduction has not been achieved.

The peritoneal surface disease severity score (PSDSS) is another useful tool that incorporates clinical symptoms, extent of carcinomatosis, radiographic PCI, and tumor histopathology (Table 23.4) [12, 16]. Although the initial use was for colon cancer with PC, its usefulness has been demonstrated in appendiceal cancer with PC, and our group has published an initial analysis on the usefulness of the stratifying system in our patients [12]. Mild symptoms are defined as weight loss of <10% body weight, mild abdominal pain, and asymptomatic ascites [16]. Severe symptoms are defined as weight loss >10% of body weight, refractory pain, bowel obstruction or symptomatic ascites [16]. A total score is calculated and correlated to a stage. A score of 2–3 points correlates to stage I disease; 4–7 points correlate to stage II disease; 8–10 points correlate to stage IV disease; and greater than 10 points correlate to stage IV disease. Patients who are stage I and II may benefit from cytoreduction and HIPEC, while stage III and IV rarely benefit from surgery.

In our institution, especially for CRC, the PSDSS is discussed preoperatively in the Tumor Board and it is shown to the patient. If the PSDSS is stage I, then we offer CRS and HIPEC upfront. In most cases if the PSDSS is stage II or above, we favor 3–6 cycles of systemic chemotherapy followed by restaging. In those who were stage II and who did not progress on systemic therapy, we then offer CRS and HIPEC. For

those stage III on presentation, if after systemic therapy their performance status allows and they did not progress, then they may be offered surgery. Stage IV PSDSS patients on presentation rarely will become operative candidates and are not considered for HIPEC.

Our institution partnered with multiple other centers to publish data examining the role of PSDSS for patients with PC from CRC. The data was very encouraging for those patients with a low PSDSS stage who underwent CRS and HIPEC. In this study 78 patients with a PSDSS stage I had a median survival of 81 months and those with PSDSS stage II ($n = 302$) had a median survival of 49 months [17]. Although the intent of the study was not to look at survival and the patient groups were quite heterogeneous, the data appears quite encouraging. As may have been expected, those in the study with a PSDSS stage IV ($n = 151$) had a median survival of only 27 months. Thus, in most cases, this survival of stage III and IV patients, which may be equivalent to those who underwent systemic therapy alone, is not long enough to advocate for CRS and HIPEC in those patients with a high PSDSS [17].

Prior Surgical Score

The majority of patients with PC will have had some type of prior surgical intervention. This is extremely important as the extent of prior surgery before CRS and HIPEC can have a negative impact on survival and increase surgical morbidity. Sugarbaker has discussed the cancer entrapment phenomenon as surgical opening of tissue planes creating raw surfaces where cancer cells will adhere, become vascularized and progress. This can make subsequent surgical cytoreduction challenging or impossible, depending on the depth of penetration of the implanted cancer cells. A PSS of 0 means no prior surgery or biopsy only. A PSS of 1 indicates 1 region of surgery, PSS 2 indicates 2–5 regions, and PSS 3 indicates more than 5 regions previously explored and dissected.

While all of these scoring and stratifying systems alone may not be enough to fully evaluate and treat a patient with PC, the combined use of the ones discussed here may allow the treating team to help standardize their approach to these patients. Most importantly, they may allow patients who will benefit the opportunity for surgery, while sparing those who will not from unnecessary exploration.

Operative Exploration/Technique

Patients who are appropriate surgical candidates benefit from radical therapy and should be brought to the operating room with curative intent. Safety and optimal cytoreduction are the primary goals. A specialized team of surgeons, nurses, anesthesiologists, perfusionists, and pathologists must work together to create an optimal, safe, beneficial procedure.

Previously diagnosed comorbidities are present in 18% of patients undergoing major oncologic resection. These morbidities increase the risk of acute medical complications (OR 3.7), in-hospital mortality (OR 3.6), hospital costs, postoperative complications (OR 3.9), and increased complication severity (OR 3.6) [8]. It becomes imperative to have preoperative optimization of these morbidities. Particular attention should be paid to patients with previous cardiac medical history. The adverse effects and risk of general anesthetic effects on cardiac function are well documented. The anesthesiologist must also take into account the duration of the procedure and the effects of hypothermia and hyperthermia. The prolonged anesthetic exposure provides additional risk. Published studies demonstrate a range of operative times for CRS + HIPEC from 433 to 470 minutes [18–20]. Patients with previous coronary artery disease, congestive heart failure, or depressed left ventricular function may not be able to tolerate prolonged or aggressive intravenous fluid resuscitation [2]. Hyperthermia-induced increases in myocardial oxygen demand can cause devastating hemodynamic compromise [2]. The American Heart Association guidelines remain the accepted standard evaluation for preoperative cardiac assessment [2].

Special consideration in this patient population is the abdominal domain. Patients with PC can have large amounts of mucinous ascites (10–15 L) that have been collected within their abdomens [2]. The increased volume and pressure can result in a decreased functional residual capacity [2]. This is a risk factor for rapid oxygen desaturation, aspiration, and prolonged ventilator requirement [2].

Patient positioning is of vital importance. The prolonged operative time increases the risk of pressure-induced wounds. All pressure points should be supported and documented as such. Additional preventive measures such as the application of sequential compression devices (SCD) should be employed. The patient may be placed supine, flat, or lithotomy; we prefer lithotomy in anticipation of low anterior resection reconstruction. Upper extremities can be outstretched or tucked as long as no traction is placed on the extremity.

Anesthesia

A close relationship with the anesthesia team is essential for the success of the patient who undergoes CRS and HIPEC. Furthermore, the experience of the anesthesia team can help improve quality and outcomes. Hemodynamic monitoring is essential for intraoperative monitoring and patient safety. We advocate the use of arterial line for accu-

rate blood pressure monitoring and selective use of central line placement for rapid administration of fluid, blood products, or inotropic support, if necessary. Some institutions do not routinely advocate the use of central line placement and we make this decision on a case-to-case basis. Although measurement of central venous pressure (CVP) does not accurately reflect volume status [2], central venous access improves the ease of serial lab draws: complete blood count, basic metabolic profile/complete metabolic profile, and coagulation studies. Close monitoring of such values allows prompt intervention and resuscitation if needed. Central lines expose the patient to potential risk: mechanical injury (pneumothorax, hematoma, bleeding, foreign body retention) and infection [2]. Other methods of estimating volume responsiveness include beat-to-beat changes in stroke volume (SV) induced by positive pressure ventilation (PPV) [2]. A small SV variation (12–13%) can indicate volume responsiveness or euvolemia [2]. We do not routinely use a pulmonary artery catheter (Swan Ganz), however, we have employed its use in thoracoabdominal HIPEC cases and when a patient has a marked preoperative cardiac history. Most recently we have employed the use of noninvasive hemodynamic monitoring systems, mainly esophageal Doppler monitoring, which has been selectively studied and used in the management of patients undergoing HIPEC. Our initial results show benefit in terms of limiting volume replacement during the intraoperative course and we plan to analyze this more closely.

Additional dynamic monitoring methods that should be employed include esophageal temperature, bladder temperature, urine output, and close attention to ventilator settings during the operation (peak airway pressure, oxygen requirements). Frequent monitoring of these parameters, in addition to those listed previously, provide dynamic information that allows the surgeon and specialized team to monitor patient safety and intervene promptly when necessary.

During HIPEC, a hyperdynamic, vasodilatory state is induced [2]. The maximum change(s) are seen from 70 to 80 minutes (of the 90-minute intraperitoneal chemotherapy) [2]. Hemodynamic changes are induced by thermal stress; this translates into increased cardiac output, decreased systemic vascular resistance, increased heart rate, and increased end-tidal carbon dioxide [2]. The increase in cardiac output is primarily driven by an increase in heart rate and not myocardial oxygen demand [2]. Esquivel et al. observed these changes with intraoperative esophageal Doppler while using the "open coliseum" operative technique [21]. Consensus guidelines from the American Society of Peritoneal Surface Malignancies now advocate for the closed abdominal technique [22]. This technique can increase intra-abdominal pressure and further exaggerate hemodynamic changes.

One of the biggest intraoperative challenges for the surgeon and anesthesiology team is fluid management. It becomes tempting to administer large amounts of crystalloid fluid in response to changes in the central venous pressures (CVP) or "third space" losses. This method can result in increased postoperative complications: pulmonary edema, adult respiratory distress syndrome (ARDS), impaired healing of anastomoses, and dilution of coagulation factors and platelets, which could result in a clinically significant coagulopathy [2]. There is good documentation that the judicious use of intraoperative fluid(s) improves outcomes after major gastrointestinal surgery [23]. Frequent laboratory draws, urine output, heart rate, ventilator parameters, stroke volume, cardiac output, and other means can all be used to provide a reasonable picture of patient status during the CRS and HIPEC. Targeted resuscitation should be emphasized with use of crystalloid fluid, synthetic colloid, and human-derived colloid (blood products). Average estimated blood loss (EBL) at our institution is approximately 240 mL, with literature citing an average EBL 300–500 mL [2]. However, with any large hemorrhage (>500 mL), volume replacement with blood products should be discussed. Additional consideration for this patient population is decreased oncotic pressure that may occur secondary to a loss in protein from surgically removed ascites. The use of synthetic colloid as replacement may need to be considered. The restrictive use of fluids during HIPEC has recently translated into improved postoperative outcomes, however, it should be stressed that adequate resuscitation and renal perfusion must also be achieved during the perfusion.

Accurate and frequent measurement of urine output is essential for hemodynamic status and renal preservation; some chemotherapeutic agents are known nephrotoxins. Ensuring adequate intravascular volume is essential as increased cardiac output and decreased vascular resistance can increase renal blood flow and renal perfusion during HIPEC [2, 24]. Dopamine was once thought to provide a nephron-protective effect by stimulation of the DA1 receptors (renal vasodilation and inhibition of proximal tubule active sodium transport) [24]. However, this is now less accepted and administration of dopamine during HIPEC is not advocated by the consensus guidelines [22]. However, we use low-dose dopamine during the perfusion in the majority of cases, but acknowledge the potential lack of benefit. If increased diuresis is needed despite adequate intravascular volume and renal perfusion, the administration of furosemide can provide additional diuresis [2]. Furthermore, the use of vasopressors to increase renal perfusion has been used during the perfusion in our and other series with acceptable return of increased urine output.

In addition to ensuring adequate volume status, electrolyte disturbances (such as potassium) must be corrected prior to administration of chemotherapeutic agents to prevent exaggerated effects due to renal losses. Certain chemotherapeutic agents can cause electrolyte disturbances. In rare

instances, oxaliplatin can predispose to a lactic acidosis, hyperglycemia, and hyponatremia [2]. Cisplatin can cause cardiac dysrhythmias (specifically ventricular tachycardia) by altered magnesium levels [25]. Additional observations comparing mitomycin C to oxaliplatin showed that patients receiving oxaliplatin had significant 24-hour postoperative hyponatremia, hyperglycemia, and metabolic acidosis, and thus strict intraoperative glycemic control is essential [26].

Furthermore, at our institution over a 24-month period we have implemented a system to monitor intra-abdominal pressure during the HIPEC. This is intended to help allow for additional data to manage the patient's volume status, hemodynamic changes, and urine output changes during the perfusion. For example, we have experienced in some cases a rapid change or decline in urine output when intra-abdominal pressures exceed 22 mm Hg and thus this monitoring allows us to adjust the pressure by changing the volume of the perfusate. Importantly, the pressure monitoring also allows us to maintain an adequate pressure that helps ensure optimal penetration of the chemotherapeutic agent being used. This work will be published in an upcoming review by the authors.

Diagnostic Laparoscopy

Traditionally, laparoscopic staging was discouraged due to difficulty in trocar placement in the presence of abdominal wall mass(es) or multiple previous surgeries, neoplastic contamination of port sites, and skepticism about the reliability of the procedure [10]. However, this is being challenged and more institutions, including ours, are performing diagnostic laparoscopy (DL) regularly. We use an open Hasson technique for laparoscopy and favor the left upper quadrant if feasible (Fig. 23.5). DL allows the surgeon to calculate the extent of disease and assess tumor burden, and determine the PCI and extent of resection needed to achieve CCR or 0/1 with less operative time, less morbidity and mortality compared to a laparotomy. DL has demonstrated multiple strengths: evaluation of small bowel mesentery, through evaluation of all regions of the PCI scoring regions; evaluation of the omental bursa, pelvic cavity, diaphragm, and abdominal wall; and allow for peritoneal washings and biopsies if needed to determine the course of treatment [10]. Its areas of inherent weakness pertain to evaluation of the thickness of diaphragmatic lesions and evaluation of pancreatic or lesser sac involvement; however, with the use of intraoperative laparoscopic ultrasound these challenges could be overcome [10].

Indications for DL include staging of PC already diagnosed via imaging, staging of PC of unknown origin, restaging following neoadjuvant therapy, restaging during follow-up with uncertain imaging, and restaging following adjuvant therapy [10].

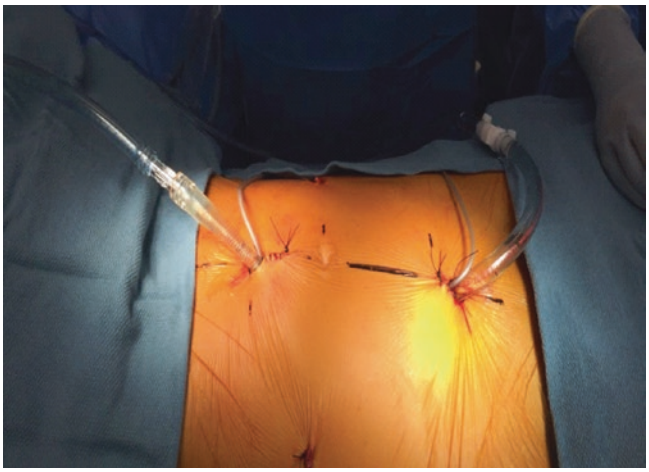


Fig. 23.5 Laparoscopic patient: our four-trocar approach to laparoscopic HIPEC in a patient with very low volume, low-grade appendiceal mucinous disease. This patient underwent laparoscopic HIPEC (shown here) and was discharged on POD 2

At our institution a patient may be brought for DL 2 weeks prior to a potential CRS + HIPEC or immediately prior to CRS + HIPEC. If a patient is brought to the operating room for diagnostic laparoscopy 2 weeks prior to potential CRS + HIPEC, he or she can be admitted as "same-day surgery" with admission and discharge the same day. Bowel preparation is usually not required. The patient is placed under general anesthetic with endotracheal intubation. Typically, patients previously have had (multiple) gastrointestinal surgical procedures; therefore using the Hasson technique to enter the abdomen is most safe in our experience. Location of entry is based on surgeon preference: periumbilical, right or left flank, right or left iliac fossa, midaxillary line, or left upper quadrant (our preferred site of entry) [10]. In our approach, once the fascia is grasped and incised, great care should be taken to dissect away any adhesions avoiding bowel injury; and once deemed safe, a large-diameter blunt Hasson port (10–12 mm) should be inserted gently and secured. Ascites should be evacuated prior to pneumoperitoneum being established [10]. If the patient has a large amount of ascites, pneumoperitoneum may be difficult to obtain without high intra-abdominal pressures. Some of these patients will be able to tolerate higher pressures due to chronic domain expansion due to ascites; however, the surgeon must be astute to subtle hemodynamic changes to indicate hemodynamic compromise and stop the procedure.

When diagnostic laparoscopy is performed immediately preceding CRS + HIPEC very little differences exist. Patients should be prepared and admitted with expectation for CRS + HIPEC to be completed. Prior to surgery, patients should have completed a bowel preparation, recent imaging (CT scan within the last 1–3 months), full laboratory work

(CBC, BMP, INR, etc.), electrocardiogram (EKG), and any other preoperative testing needed to optimize the patient.

Upon visualization of the abdomen, each quadrant of the abdomen and the entire peritoneum should be visualized if possible and a PCI calculated. The patient should be rotated into at least four different positions to fully inspect the abdomen: steep reverse Trendelenburg left tilt, steep reverse Trendelenburg right tilt, steep Trendelenburg right tilt, and steep Trendelenburg left tilt [10].

In one report, diagnostic laparoscopy was performed in 351 patients with 99.7% of patients having successful staging [10]. Only 1 patient (0.28%) was not able to undergo laparoscopy staging due to dense adhesions [2]. Five patients were under staged (1.4%) which became evident upon laparotomy and resulted in incomplete cytoreduction [10]. There were two site infections, one episode of bleeding, one bowel perforation, one diaphragm perforation, and zero mortality [10]. No neoplastic seeding was detected or any port site metastases [10].

The algorithm for proceeding with CRS + HIPEC after DL is outlined in Fig. 23.6 [10]. This algorithm is based on a combination of absolute exclusion criteria and relative inclusion criteria if a patient has an acceptable PCI on DL.

If the patient is not a candidate for CRS + HIPEC, the patient can be discharged that day with short-term follow-up in the office to discuss surgical findings and referral to medical oncologist. If the patient is eligible for and able to complete further systemic treatments, they can then at that point be brought back to the surgeon's office for re-evaluation and restaging. We prefer performing diagnostic laparoscopy in a separate setting before the intended CRS and HIPEC, especially for high-grade histologies. This helps limit the mobilization of extensive resources for the major procedure when the diagnostic laparoscopy reveals an unresectable burden of disease.

Cytoreductive Surgery

If a patient is deemed an acceptable candidate for CRS + HIPEC after laparoscopic evaluation, the pneumoperitoneum is evacuated, trocars removed, and laparotomy performed via midline incision. In some patients with very limited disease (PCI <10), laparoscopic cytoreductive surgery may be possible [27, 28]. Esquivel et al. demonstrated that in patients with limited disease, laparoscopic cytoreduction is feasible and safe [27]. A European study showed that when comparing laparoscopic versus open procedures, compete cytoreduction was possible without conversion to open [28]. The laparoscopic group had a shorter mean operative time (210 versus 240 minutes), shorter mean length of stay (12 versus 19 days), and fewer grade III/IV complications (one versus four) [28].

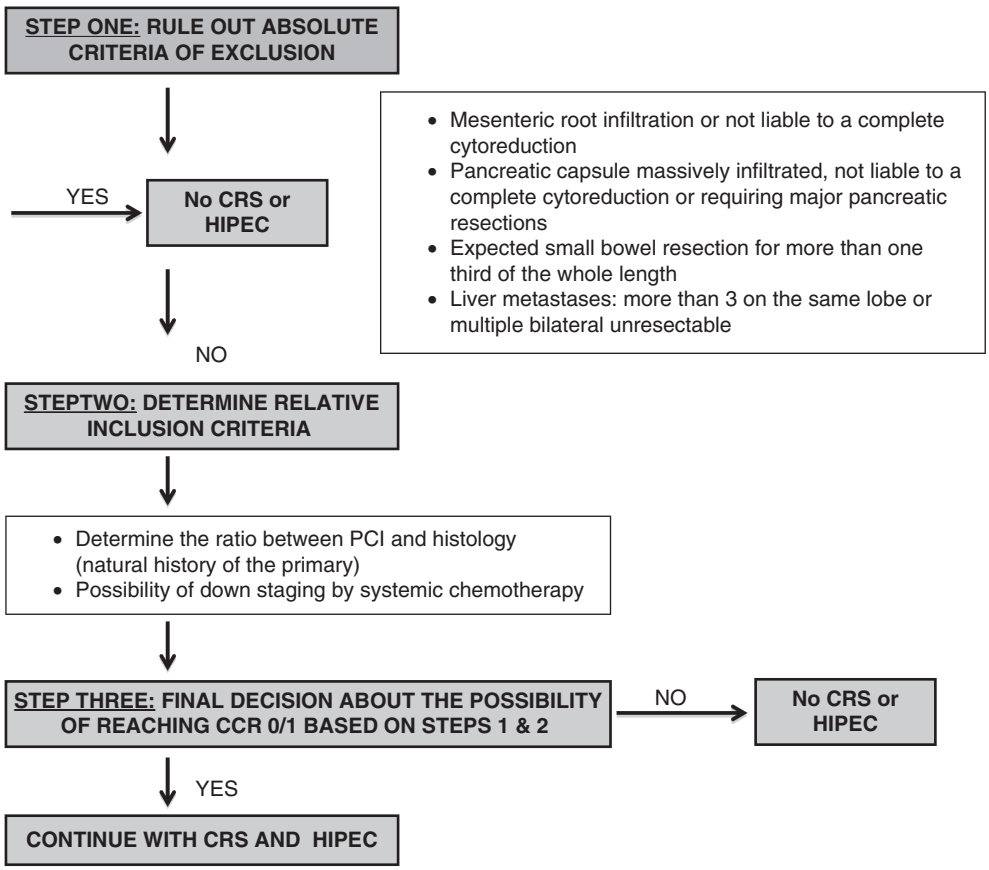


Fig. 23.6 As from Valle et al. [10], algorithm for decision-making process for a correct indication for radical CRS + HIPEC based on laparoscopic staging

To proceed with laparotomy for CRS, a midline incision is extended superiorly to the xiphoid (which we routinely resect) and inferiorly elliptically around the umbilicus (which is resected) to the pubis. Great care must be taken when entering the abdomen to prevent inadvertent organ injury. Upon entrance into the abdomen, a thorough manual inspection should be performed. The surgeon should evaluate all regions: the retrohepatic space, the lesser sac, the splenorenal fossa, the pelvis, small bowel, the mesentery, and entire peritoneum. If there is an acceptable PCI (<20) in patients with invasive disease, then cytoreductive surgery (CRS) with curative intent should proceed; this, of course, depends on the primary histology.

A large-caliber, self-retaining retractor that exposes the entire abdomen should be utilized. In our practice the Thompson liver retractor (Thompson Surgical Instruments, Inc., Traverse City, MI) is utilized to expose the entire abdomen. Surgeons should also take into consideration the tools that are used to resect tumor. Traditional scissor and knife resections can cause profuse bleeding from peritonectomy and cause a large dissemination of malignant cells within the abdomen [29]. The use of electrocautery/electroevaporative surgery should be implemented. A zone of heat necrosis (at the margin of resection) is caused by high-voltage electrocautery, which destroys all malignant cells within this zone [29].

Lysis of all adhesions should precede for all peritonectomies or visceral resections. It is theorized that malignant cells are trapped within adhesions, which are not penetrated by the chemoperfusate [29]. The "tumor cell entrapment hypothesis" is a mechanism whereby malignant cells are fixed at sites of prior surgical dissection [29]. It is therefore of vital importance to take down all adhesions and preserve bowel integrity as much as technically possible.

Cytoreductive surgery for peritoneal malignancies includes resection of primary tumor(s) and all metastases; this may include the entire peritoneum. Up to five procedures may be needed to achieve resection of the peritoneum that is involved with the malignancy [29]. The peritonectomy procedures include: anterior parietal, left upper quadrant, right upper quadrant, pelvic, and omental bursectomy [29]. Please see Table 23.5 for the resection regions achieved by each peritonectomy [29].

Both parietal and visceral peritoneum may need resection; however, when the visceral peritoneum is involved the underlying organ (stomach, small bowel) requires coinciding resection [29]. The visceral peritoneum is involved most commonly in three locations: the rectosigmoid colon, ileocecal valve, and antrum of the stomach [29]. These three locations are sites where the bowel and retroperitoneum have a particularly strong attachment with less peristalsis of the visceral peritoneum allowing more time for tumor deposition [29]. A complete pelvic peritonectomy is most often required:

Table 23.5 The five different peritonectomy procedures and their regions of resection for each

Peritonectomy procedures	Resection regions
Anterior parietal	Epigastric fat pad, umbilicus, and previous incisions of the abdomen
Left upper quadrant	Greater omentum and spleen
Right upper quadrant	Tumor on Glisson's capsule
Pelvic peritonectomy	Uterus, ovaries and rectosigmoid junction
Omental bursectomy	Gallbladder and lesser omentum

Modified from Sugarbaker [29]

stripping of all sidewalls, peritoneum overlying the bladder, the cul-de-sac, and resection of the rectosigmoid colon [29]. Resection of the ileocecal valve along with the distal most terminal ileum is often required [29]. The pylorus of the stomach is fixed to the retroperitoneum, and tumor may collect in the subpyloric space via the foramen of Winslow [29]. Large amounts of disease in this area may cause gastric outlet obstruction [29].

Multiple additional procedures may need to be performed to obtain CCR 0/1. If a (right or left) subdiaphragmatic peritonectomy is to be performed, we advocate for xiphoidectomy prior to the peritonectomy [29]. The xiphoid is exposed back to its origin at the base of the sternum using electrocautery, which has twofold importance in this area: to control arterial bleeding that is located lateral to the xiphoid and to allow easier fracture of the xiphoid due to denatured bone proteins [29]. The xiphoid can be grasped with a Kocher clamp or similar tool and fractured away sharply from the base of the sternum.

Alternatively, we prefer that after dissection through the abdominal wall, prior to entrance into the abdomen, the surgeon dissect the parietal peritoneum off the retrorectus sheath. This leaves the anterior peritoneum intact and a small peritoneal window at the superior aspect of the incision can be created (Fig. 23.7). This will allow the surgeon to inspect and palpate the anterior parietal peritoneum and assess if a total or partial anterior parietal peritonectomy is needed [29]. Dissection should continue superiorly to the undersurface of the hemidiaphragm(s) down toward the paracolic gutters [10]. The section of the parietal peritoneum in closest attachment with the underlying tissue is along the transverses muscle. Dissection is more difficult here compared to the looser connections along lines of Toldt along the paracolic sulcus [10]. If cancer nodules are palpated, a complete anterior peritonectomy is required; if no nodules are palpated, then the anterior peritoneum can be maintained with only regional resections.

A left subphrenic peritonectomy is begun by dissection of the epigastric fat pad and peritoneum off the posterior rectus

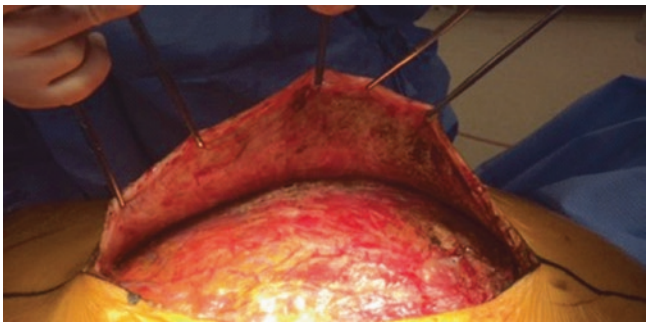


Fig. 23.7 Anterior parietal peritonectomy in our patient with a low-grade appendiceal mucinous carcinomatosis with large volume mucinous ascites

sheath [29]. Dissection continues with electrocautery to separate the peritoneum from the diaphragm, left adrenal gland, and superior portion of the perinephric tissue [29]. The splenic flexure of the colon should be mobilized medially by transection of the peritoneum along the lines of Toldt [29]. The stomach (after ligation and transection of all of the short gastric arteries) can be reflected medially to allow visualization of the left adrenal gland, pancreas, the anterior surface of the transverse mesocolon, and perinephric tissues [29]. The left lateral liver should be mobilized, with care not to injure the inferior phrenic vein, which can be ligated and divided if needed to perform inclusive peritonectomy. At this point we also incise the pars flaccida to allow access to the lesser omentum and caudate liver, which should be explored thoroughly. Blood vessels that are encountered during dissection of the diaphragm should be well controlled prior to division, for these vessels tend to retract into the diaphragm muscle, which can be a source for ongoing hemorrhage [29].

A right subphrenic peritonectomy begins similar to that of the left: from the right posterior rectus sheath. Dissection should be continued in the same manner, using high voltage 3 mm ball tip electrocautery, taking care to control all vessels encountered. To ensure complete peritonectomy, mobilization of the liver must be extensive and gentle downward retraction should be used so as to not damage the liver or its vascular attachments. The right peritonectomy is continued until the bare area of the liver is reached [29]. The peritoneum should be followed onto the liver surface as Glisson's capsule. All of the capsule and associated tumor should be removed. It is possible to remove a thick layer of tumor with little blood loss by using electrocautery beneath Glisson's capsule [29]. Complete removal of the falciform ligament, most importantly at this area of hepatic attachment, is necessary. Not only is tumor deposition along the falciform ligament encountered, but at its entrance in the hepatic parenchyma it is covered in peritoneum, creating a tunnel with potential tumor deposition [29]. In some patients a bridge of hepatic tissue covers the entrance; this bridge must be divided to allow full inspection of this area of peritoneum [29]. This is often in close proximity to the left hepatic artery, so careful, direct dissection must occur [29]. See Fig. 23.8 for right upper quadrant peritonectomy intraoperative and completion.

Lateral dissection over the perinephric tissues and right adrenal gland should also be completed [29]. If tumor is densely adherent to or invading the tendinous portion of the diaphragm, that section should be resected using an elliptical excision and promptly repaired with a strong nonabsorbable 0 suture [29].

Removal of the gallbladder should occur in standard fundus down technique. Once the cystic duct and cystic artery are ligated, the tumor overlying the hepatoduodenal ligament can be removed [29]. Oftentimes, tumor is heavily layered over the ligament, but this can be dissected away bluntly [29]. However, thick deposits of tumor can make cystic dissection difficult due to skewed anatomy.

We prefer to encircle the porta hepatis and then dissect out all structures as the tumor is dissected away. The lesser omentum is resected with preservation of the right gastric artery [29]. One must inspect for the presence of a replaced or accessory left hepatic artery coming from the left gastric artery. This must be preserved unless embedded in tumor and its preservation would prevent a complete cytoreduction [29]. The gastrohepatic ligament is separated from its hepatic attachments at segments 2 and 3, with careful dissection around the caudate lobe to not disrupt its delicate blood vessels, which has its origins along the anterior surface of those segments [29]. The peritoneum and lesser omentum is divided along the lesser curvature of the stomach [29]. It is separated from the vascular and vagal arcades toward the left gastric artery and subsequently released [29].

Reflection of the left liver can allow the surgeon to visualize the posterior aspect of the hepatoduodenal ligament and omental bursa. The peritoneum overlying the left liver extending to the subhepatic vena cava is divided. Blunt dissection can then be used to strip the peritoneum from the superior recess of the omental bursa, the crus of the right diaphragm, and beneath the portal vein [29].

A complete pelvic peritonectomy includes resection of the uterus, ovaries, rectosigmoid colon, and peritoneum [29]. Pelvic peritonectomy begins with resection of the peritoneum from the inferior aspect of the abdominal incision. Dissection is continued to the right and left borders of the bladder [29]. The peritoneum overlying the surface of the bladder is stripped away to the level of the cervix or seminal vesicles while counter traction is placed on the urachus [29]. The proper plane for dissection is between the musculature of the bladder and its overlying fatty tissue [29]. Both uterine arteries are ligated close to the base of the bladder, just above the ureters [29]. Laterally, the peritoneum is continuous with the peritoneum of the right and left

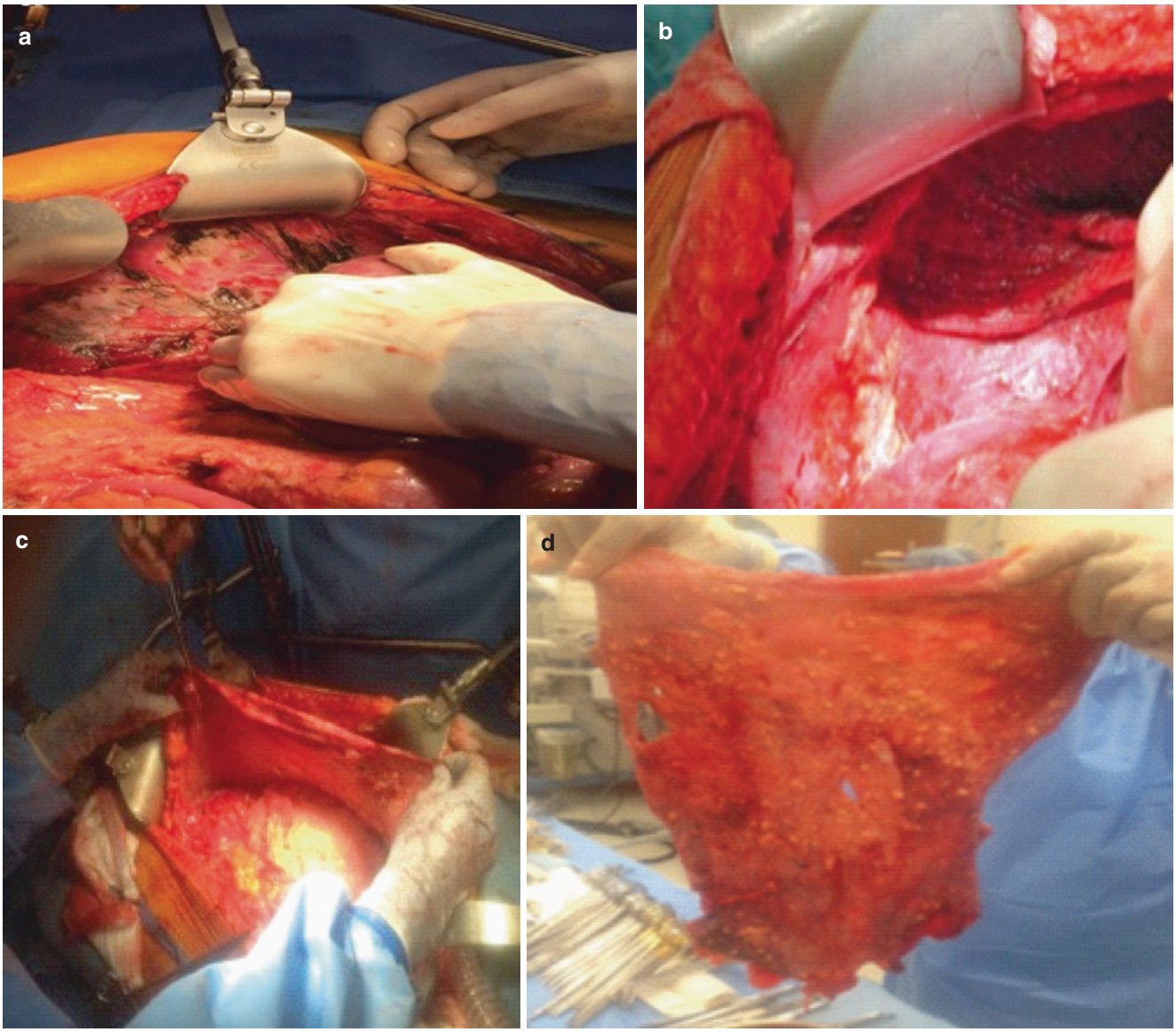


Fig. 23.8 (**a**, **b**) Retraction of the liver demonstrating the right upper quadrant peritonectomy site. (**c**) Left upper quadrant/abdominal wall peritoneum. (**d**) The right upper quadrant with liver retraction demonstrating a complete peritonectomy and the removed specimen

paracolic sulci [29]. Care must be taken not to damage the ureters. In females, the round ligament is identified and ligated as it enters the internal inguinal ring [29]. Both ovarian veins are ligated at the level of the lower pole of the kidney [29]. If tumor burden is present beyond local resection, the rectosigmoid colon is formally resected just distal to the pelvic tumor [29]. Electrocautery is used to excise the mesorectum circumferentially [29]. Exposure of the rectovaginal septum is then achieved by dissecting the bladder away from the cervix where the anterior and posterior vaginal cuff is transected [29]. The perirectal adipose is divided beneath the peritoneal reflection to ensure removal of all tumor within the cul-de-sac [29]. See Fig. 23.9 for pelvic peritonectomy.

Small bowel involvement may be extensive or focal. There are five types of small bowel involvement based on size and invasiveness. See Table 23.6 [30].

Type 1 nodules are small in size, do not invade past the peritoneum and have a less aggressive histology [29]. The small size of these nodules are amenable to resection using scissors and do not require resection of the small bowel wall [29]. Type 2 lesions require a partial thickness resection of the bowel wall due to invasion into the muscular layer [29]. Mucosa and submucosa are left intact and the seromuscular layer is repaired primarily [29]. These nodules are preferentially removed via scissor dissection. Type 3 nodules are large enough that a full-thickness resection of the antimesenteric bowel wall is needed [29]. The defect is

repaired in a two-layered fashion. Type 4 nodules can undergo localized resection or segmental small bowel resection pending the size (of the nodule) and vascular supply [29]. A two-layered repair follows the localized resection, and a hand sewn end-to-end or stapled side-to-side small bowel anastomoses are performed for segmental resection. Type 5 nodules require a formal small bowel resection with associated mesentery (Fig. 23.10) [29]. The section of small bowel and mesentery that is resected is divided with a linear stapler.

Currently there is no consensus if anastomoses should occur prior to or after chemoperfusion of the abdominal cavity. We routinely perform all anastomoses after perfusion. The only agreed upon closure prior to HIPEC is that of the vaginal cuff to prevent leakage. An observational study over a 10-year period demonstrated no difference in the development of digestive fistulas in patients who had anastomoses performed prior to (26%) or after (74%) HIPEC was performed [31]. Full bowel resections with primary anastomoses should be completed after HIPEC (i.e., type 5 small bowel nodules). In our center all bowel anastomoses are performed after HIPEC.

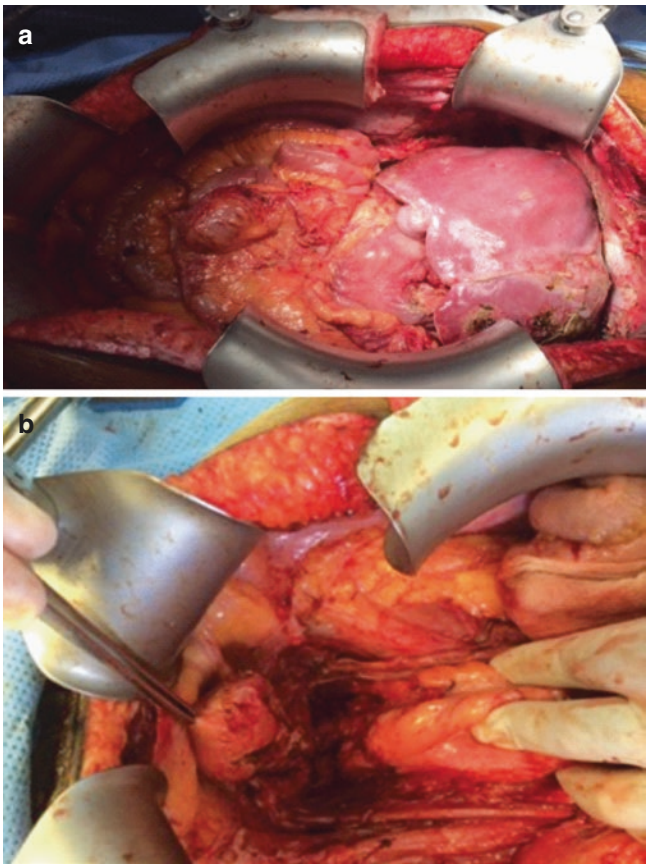


Fig. 23.9 (**a**, **b**) View into the pelvis demonstrating complete removal of pelvic peritonectomy and abdominal view after complete cytoreduction

Table 23.6 The five types of small bowel involvement

Nodule type	Description
Type 1	Noninvasive nodule
Type 2	Small invasive nodules on the anti-mesenteric portion of the small bowel
Type 3	Moderate sized invasive nodules on the anti-mesenteric portion of the small bowel
Type 4	All sizes of invasive nodules at the junction of small bowel and its mesentery
Type 5	Large invasive nodules

Modified with permission from Bijelic and Sugarbaker [30]

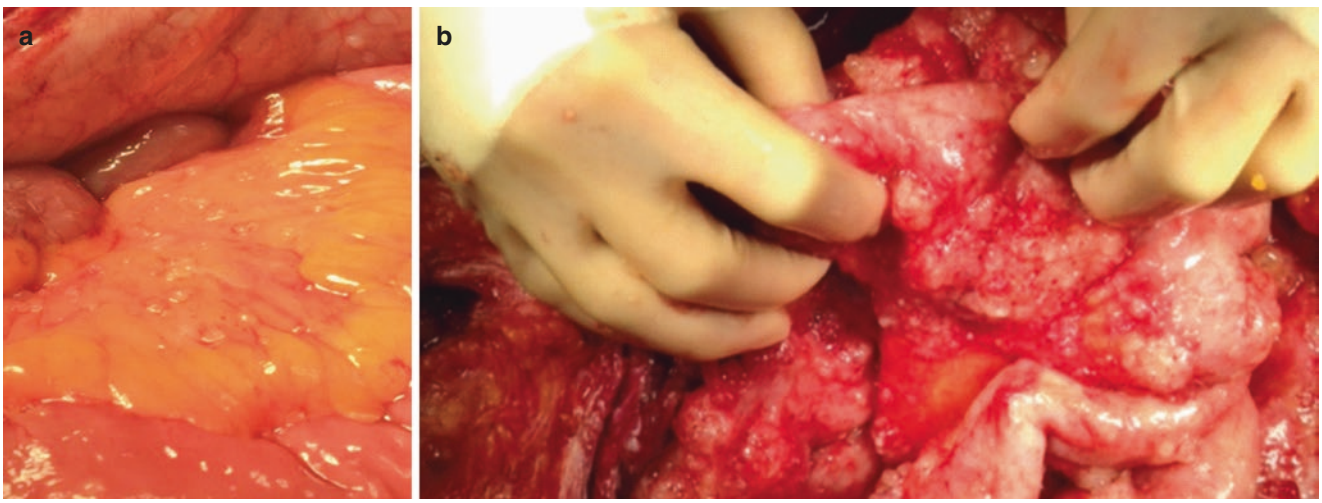


Fig. 23.10 (**a**) Small noninvasive resectable nodules in small bowel mesentery. (**b**) Invasive nodules of various sizes on the small bowel

Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Once a CCR 0/1 has been achieved, the team can begin to prepare for instillation of the chemoperfusate. HIPEC should achieve total destruction of all microscopic in situ malignant cells. Animal models have supported a "peritoneum-tumor" barrier composed of the peritoneal mesothelium, the extracellular matrix that surrounds the tumor and successive layers of tumor cells [32]. This barrier is a limiting factor for penetration of the chemoperfusate into the tumor.

In previous literature, multiple different techniques to perform HIPEC have been described. Variability existed from institution to institution based on HIPEC method (open coliseum, partial closure, peritoneal cavity expander, closed), drug(s) used, dosage of drug(s), timing of drug delivery, volume of perfusate, inflow temperature, and duration of perfusion.

The American Society of Peritoneal Surface Malignancies (ASPSM) was created to develop standardized methods of patient selection and therapy guidelines to maximize benefit while minimizing morbidity and overtreatment of this diverse patient population [22]. As of 2017, the ASPSM had 240 members from 26 countries [33]. When established in 2009, the first goal of the ASPSM was to establish standardization of HIPEC delivery in the United States of America for multiple disease processes (colorectal cancer, ovarian cancer, peritoneal mesothelioma, low-grade appendiceal, and high-grade appendiceal cancers) [22, 33]. To date, the consensus guidelines on HIPEC delivery for use in colorectal cancer with peritoneal dissemination have been published [22].

Traditionally, three methods of HIPEC delivery have been described: open coliseum technique, the peritoneal cavity expander (PCE), and closed technique [2]. Although most centers now perform exclusively closed technique, we will briefly mention the open coliseum and PCE techniques. The open method, often referred to as the coliseum technique, was originally described by Sugarbaker upon completion of CRS, four watertight closed outflow suction drains are anchored through the abdominal wall [2]. These drains remain in place in the postoperative period [2]. An inflow line is placed over the open abdomen into the peritoneal cavity along with accompanying temperature probes [2]. The abdominal incision skin edges are suspended to create a self-retaining column with the surgical retractor (Fig. 23.11) [34, 35]. A plastic sheet is placed over the abdominal opening that contains a small incision to allow the surgeons to manually stir the cavity [2]. Personal protection equipment is of vital importance to surgeon safety with this technique (double glove, goggles, imperforate gown, etc.) [2].

The peritoneal cavity expander is a variation of the open coliseum technique that was utilized in Japan without much popularity elsewhere [2, 36]. This method utilizes an acrylic cylinder with inflow and outflow lines that are secured over the abdominal incision [2, 36, 37]. See Figure 23.12 [36]. When the expander is filled with perfusate, it allows the small bowel to float, allowing it to be manipulated [2].

The closed technique is the method most widely practiced and described in the ASPSM consensus guidelines. Once cytoreduction has been achieved, the abdomen is thoroughly irrigated to remove any cellular debris. Perfusion cannulas are attached to inflow catheters with a watertight 0 silk suture (or similar suture). Temperature and pressure probes are attached to the cannulas with a suture in a similar fashion. Inflow and outflow catheters are placed under the diaphragm and into the pelvis. The tubing must lie easily without kinks or sharp bends. The laparotomy incision is then closed, watertight, around the cannulas, creating a closed circuit.

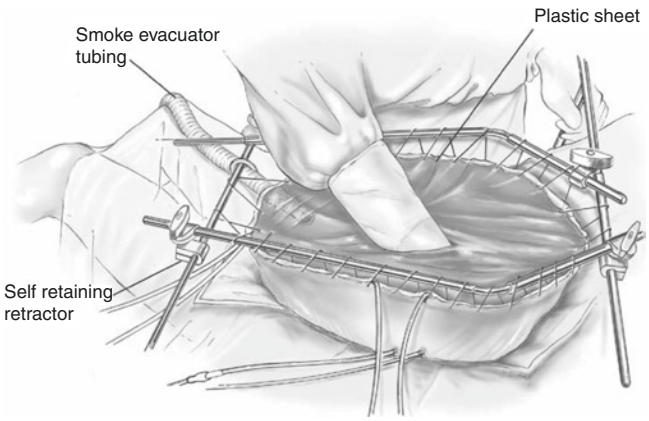


Fig. 23.11 Demonstration of the open coliseum HIPEC technique. (Reprinted with permission from Esquivel et al. [35])

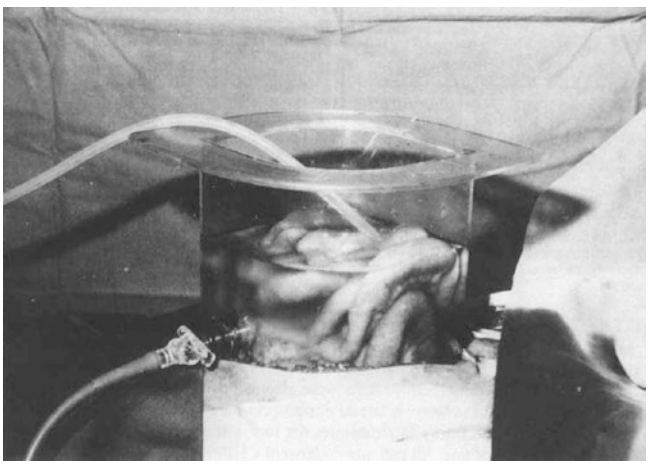


Fig. 23.12 Demonstration of the peritoneal cavity expander HIPEC technique. (Reprinted with permission from Fujimura et al. [36])

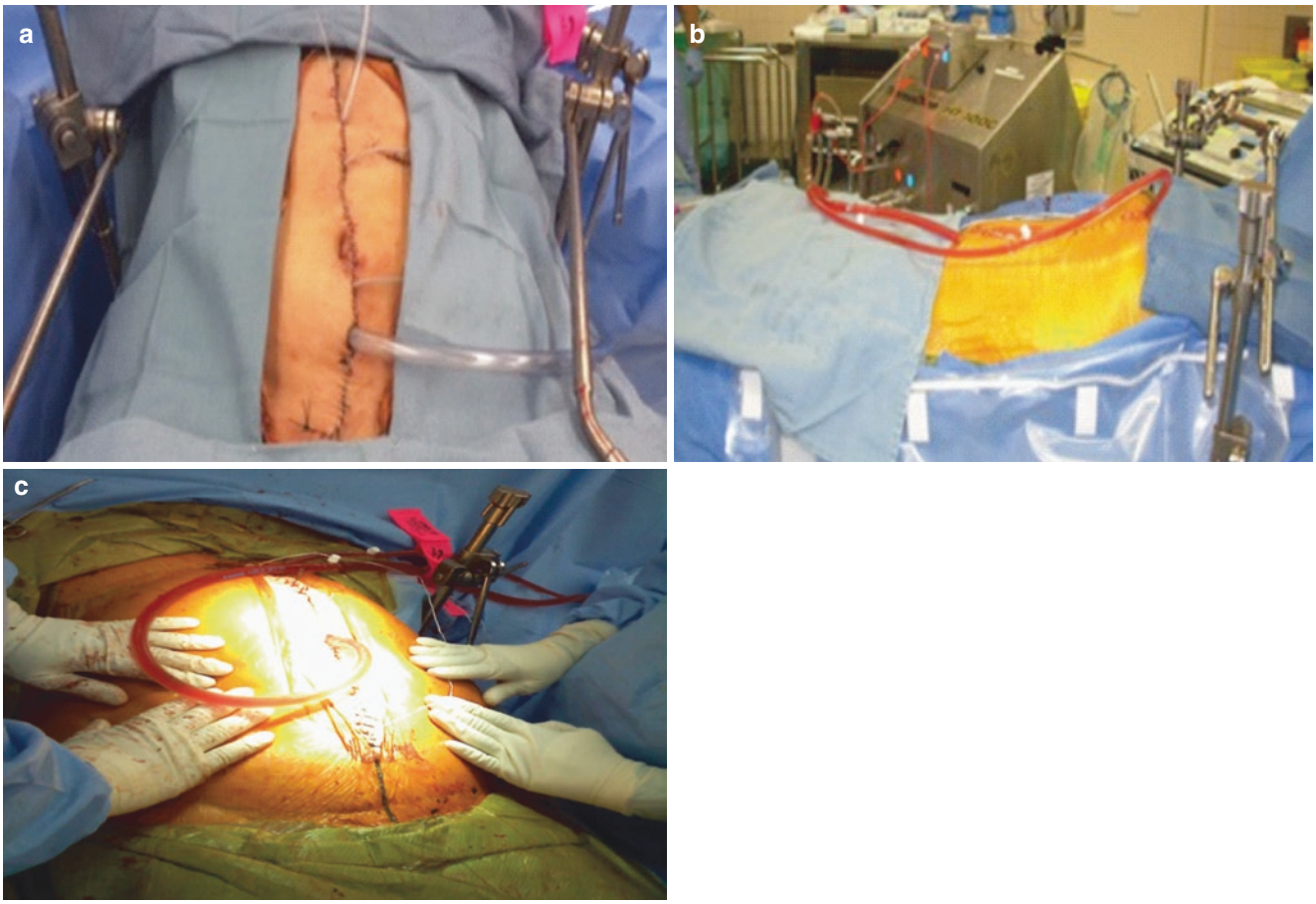


Fig. 23.13 The closed technique. (**a**, **b**) The abdomen is temporarily closed with cannulas, temperature probes, and pressure probes incorporated. (**c**) The abdomen is gently agitated

See Fig. 23.13. The abdomen undergoes gentle external agitation to promote fluid circulation and even distribution of the perfusate. The closed technique requires a larger volume of perfusate and a higher abdominal pressure [2]. This may improve perfusate drug penetration into malignant cells [2]. At the end of HIPEC, the cavity is drained and laparotomy incision reopened; anastomoses are then performed [2].

At our institution we perform a 90-minute perfusion with mitomycin C at a 42 °C inflow temperature for colorectal and appendiceal cancer and a 60-minute perfusion when using cisplatin for peritoneal mesothelioma, gastric, and ovarian cancer.

Chemotherapeutic Drugs

The drug chosen as the chemoperfusant should pose demonstrable activity against the malignancy being treated. The drug must also be directly cytotoxic; drugs needing systemic metabolization into their active form are not appropriate for use with HIPEC [38]. The ideal agent will possess direct cytotoxic activity synergistic with heat, lack local toxicity, without systemic spread, or systemic toxicity [38]. Tumor specificity should be considered: Previous responses to systemic agents may indicate tumor sensitivity or resistance to intraperitoneal agents. Toxicities of the drug chosen is influenced by the drug concentration to the maximal plasma drug concentration [38]. This creates a concentration-time curve gradient and the area under the curve helps dictate maximal doses [38].

The intraperitoneal route will deliver high regional concentrations with minimal systemic effect due to the "peritoneal-plasma" barrier [38]. This barrier maintains minimal displacement of the drug from the peritoneum to the plasma [38]. Limited and delayed absorption through the peritoneum is more pronounced with high-molecular weight

molecules; therefore these drugs are more favorable for use in HIPEC [38]. Additionally, any drug that is absorbed into the visceral peritoneum will be drained via the portal system and undergo first pass metabolism in the liver, therefore inactivating the drug and minimizing systemic exposure [38]. Renal excretion of the metabolites is usually rapid. The most common presentation of systemic toxicity is bone marrow suppression [38].

Intraperitoneal drug concentration and exposure to the drug are the two biggest determinants that affect treatment [38]. Drug concentration refers to concentration in the peritoneum or tumor cells; concentration of drug in the perfusate fluid is of less importance [38]. Increased local concentration in tissues will improve penetration, and, although this is difficult to measure, the depth of penetration is estimated to be 2–5 mm [38].

Heat alone has a direct antitumor effect. Application of heat causes protein denaturation, impaired DNA repair, inhibition of oxidative metabolism causing cellular acidity, lysosomal activation, and increased apoptosis [2]. Heat shock proteins may limit these direct hyperthermic effects.

The combination of hyperthermia (temperatures above 39–40 °C) and neoplastic drug(s) results in exponential increase in cytotoxic effect [38]. This is dependent upon multiple factors: increased uptake into malignant cells, increased membrane permeability, improved membrane transport, alteration of drug metabolism (decreased adenosine triphosphate transporters allowing drug accumulation), excretion, drug penetration, drug action, and inhibition of repair mechanisms [2, 38]. Heat stability of the drug is a requirement. We will discuss drugs used for each malignancy in the following sections.

In our institution we use mitomycin C (40 mg dose, given in two doses, 30 mg at time zero/10 mg at time 60 minutes) for appendiceal and colorectal primaries. For gastric cancer, ovarian cancer, and mesothelioma, we use a combination of cisplatin and doxorubicin. In patients with recurrence from appendiceal and colorectal cancer who present and are candidates for a second debulking and HIPEC, we use melphalan (60 mg/m^2 for 60 minutes) and have had favorable, safe results.

Appendiceal Cancer

Cancer of the appendix is rare, with approximately 1% of appendectomy specimens harboring malignancy. Approximately 200–1000 new cases are reported each year, which correlates to 0.12 cases per 1,000,000 of population [2]. Adenocarcinoma was diagnosed in approximately 65% of new cases. Traditionally, these patients were treated with systemic chemotherapy and some debulking procedures. This would fail to eradicate the microscopic disease and recurrences would occur in more than 90% [2].

Prognosis is determined by histologic grade, tumor biology, age, functional status, and extent of disease at diagnosis [2]. Patients may present with copious intraabdominal mucin—pseudomyxoma peritonei (any primary tumor with copious intraperitoneal mucin production) [2]. However, patients may present without mucin and demonstrate solid peritoneal disease that shows minimal differences from other gastrointestinal malignancies [2]. Sugarbaker and his colleagues first described a new approach in 1980 with CRS combined with hyperthermic intraperitoneal chemotherapy, which has now become the standard of care for treatment of peritoneal dissemination from appendiceal neoplasm [2].

Patients will be diagnosed either inadvertently after surgery or with late systemic or peritoneal disease [2]. These malignancies are classified as either “low grade” or “high grade”; however, there is documentation of differentiation of low-grade malignancies into high-grade lesions in about 16% of patients [2]. This suggests that these malignancies lie on a spectrum rather than definitive categories. Pattern of spread is related to the grade of disease [2].

Luminal obstruction, usually by mucin, is the first step in disease dissemination of low-grade tumors (Fig. 23.14). Excessive mucin production occludes the lumen, which increases pressure and causes perforation of the appendix with peritoneal dissemination of mucin and tumor cells. Low-grade lesions are associated with implantation and spread along the peritoneal surface in a predictable sequence: right lower quadrant, the pelvis, the right upper quadrant, and finally throughout the abdomen [2]. Distant or lymphatic metastases occurs in less than 10% of cases [2].

Most centers use mitomycin C for appendiceal tumors. Mitomycin C has good activity against gastrointestinal malignancies as an alkylating antibiotic [38]. It has acceptable tumor penetration (2–5 mm) and an intraperitoneal to plasma drug area under the curve (AUC) ratio of 13–80, indicating good pharmacokinetics and low systemic toxicity [38]. Oxaliplatin has been used in high doses over short intervals (30 minutes). In some institutions, systemic 5-fluorouracil and leucovorin are simultaneously administered to enhance oxaliplatin therapy [38]. There is rapid absorption of the drug into the tumor, although with a low AUC: 13 [38].

Outcomes vary depending on histology, the extent of peritoneal seeding, and comorbidites [2]. Mucin-

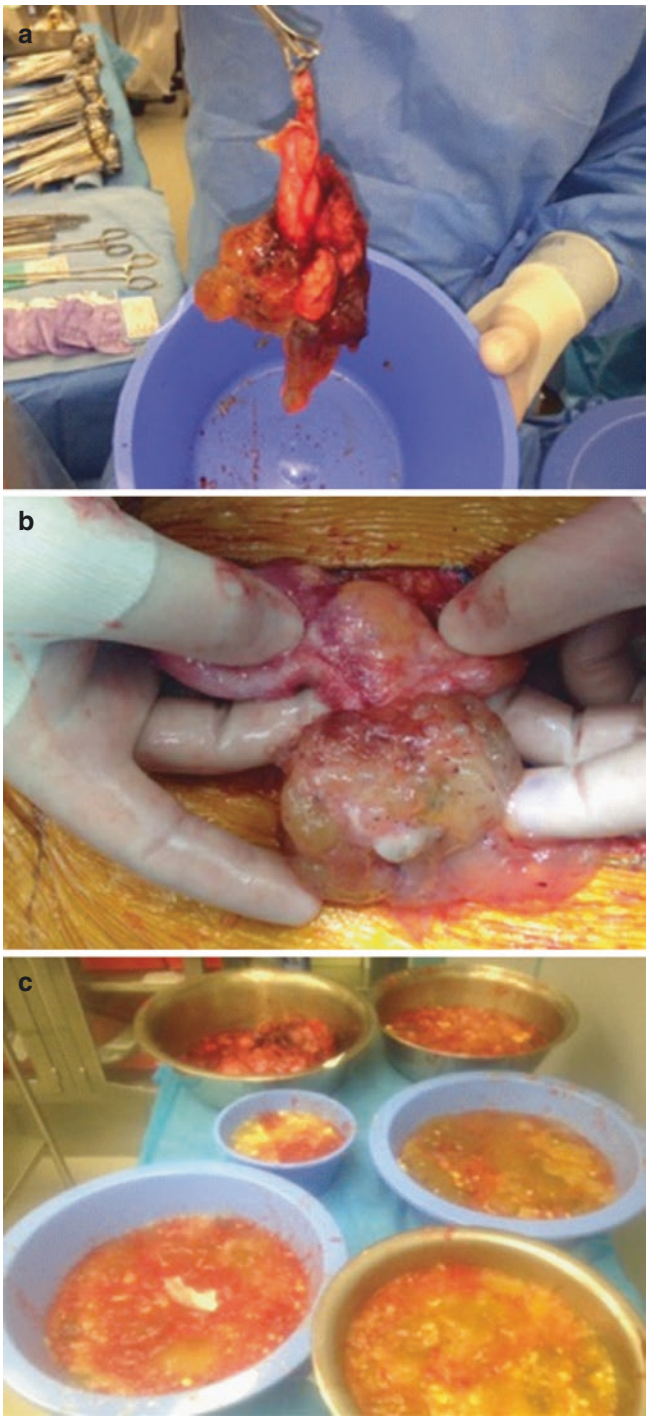


Fig. 23.14 (**a**, **b**) Demonstrating the appendix with tumor and mucin production, and (**c**) mucinous fluid from a patient with a low-grade mucinous neoplasm

Table 23.7 General principles for treatment of low- and high-grade appendiceal mucinous neoplasms

Histology	LAMN	High-grade
Debulking and HIPEC	Yes	Yes
Systemic chemotherapy	No (usually)	Yes
Right colectomy	No	Yes
Median survival	~10 years	~2 years
LN/distant metastasis	No	Yes

LAMN low-grade appendiceal mucinous neoplasm, *HIPEC* hyperthermic intraperitoneal chemotherapy, *LN* lymph node

producing tumors generally have a more predictable clinical course (peritoneal dissemination) and a better response to therapy [2].

In our series, and in most throughout the nation, the most common reason for cytoreduction and HIPEC is an appendiceal neoplasm. The grade of the appendiceal tumor is of utmost importance, and in general all low-grade mucinous neoplasms of the appendix may be treated with debulking and HIPEC if needed. We know that this group of patients, if optimally cytoreduced and administered HIPEC, has the best prognoses with median survival exceeding 10 years in most series. This is highly dependent on the grade of the neoplasm and perhaps even the molecular profile of the tumor, as even low-grade tumors with certain molecular mutations may behave aggressively. High-grade neoplasms, as defined by Misradji, can behave as an aggressive invasive malignancy. Thus, the management of high- and low-grade appendiceal mucinous tumors may differ depending on the clinical presentation. When we evaluate a patient with a low-grade appendiceal mucinous neoplasm (LAMN), the expected thorough evaluation includes a detailed history and physical examination, laboratory evaluation (including CEA, CA 19-9, and CA-125), review of operative and pathology notes, imaging (CT, MRI, PET), and functional performance status. Some general, although not completely inclusive, principles can help define the course of treatment (Table 23.7).

Furthermore, Sugarbaker and colleagues have recently defined the role of right colectomy and based this on histology of the primary as shown in Fig. 23.15 [39].

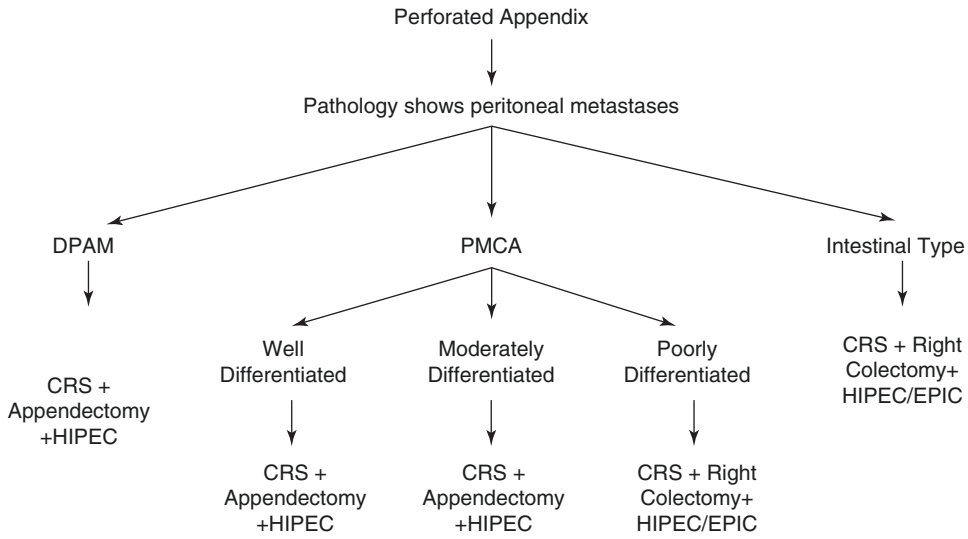


Fig. 23.15 When should a right colectomy be performed? Proposed algorithm for management of perforated appendiceal epithelial neoplasm. (Reprinted with permission from Sugarbaker [39])

Gastric Cancer

Gastric cancer accounts for the third most common cause of malignancy-related death (8.8% each year). The presence of peritoneal dissemination with gastric cancer is a sign of advanced tumor stage, progression, and disease recurrence [2]. Risk factors for gastric peritoneal carcinomatosis (GPC) include advanced T stage (serosal involvement), advanced nodal status, tumor size, young age, female gender, signet ring cell histology, and diffuse mixed histology [40]. It is estimated that in 5–43% of patients who undergo resection with curative intent of the primary tumor, peritoneal dissemination is already present [2, 40]. Additionally, peritoneal carcinomatosis is the most common synchronous lesion (35%) [40]. After gastrectomy with D2 lymphadenectomy, peritoneal recurrence occurred in 10–50% of patients (with peritoneum being the sole site of recurrence in 12–40%) and distant metastases in 25% of patients [40, 41]. This is clearly an indicator of poor prognosis with average time to death of 3–7 months [40, 42]. Systemic chemotherapy regimens only marginally improved survival: 9.5–12 months [40].

Gastric peritoneal carcinomastosis (GPC) occurs with a high frequency due to the tendency of gastric cancer to produce intraperitoneal free cancer cells [40]. These free cells can be found in 24% of stage I disease and 40% of stage II or III gastric cancer [40]. The occurrence increases if the malignancy involves the serosa [40]. Traumatic release from surgical manipulation also contributes to intraperitoneal free cancer cells [40]. These cells are released from surrounding lymphatic channels, blood loss within the surgical field, and resection margins [40]. The number of peritoneal lavage specimens positive for malignant cells doubled after gastrectomy (24% before, 58% after) [43]. Cells released adhere to exposed surgical surfaces within minutes due to the local release of cytokines, fibrin, and other adhesion molecules [44]. This creates a localized hypoxic environment rendering the cells relatively immune from systemic chemotherapy, thus HIPEC is targeted to these cells.

HIPEC has been used for prophylaxis against PC or adjuvant treatment in gastric cancer. Prophylactic use allows free cells to be washed out with destruction of adhered cells by the synergist effect of chemotherapy and heat [40]. Most of the published literature has been conducted in Asian countries. Some of the earlier studies demonstrate a 3-year survival rate (74% versus 53%) and decreased occurrence of peritoneal recurrence (36% versus 50%) in patients who received prophylactic HIPEC [45]. More studies have demonstrated a survival advantage for patients undergoing HIPEC as prophylactic treatment for PC (Table 23.8) [36, 40, 45–51].

Therapeutic HIPEC has demonstrated survival benefit over CRS alone. Drugs that are commonly used include mitomycin C, cisplatin, and etoposide (in decreasing order). Studies that employed mitomycin C during their HIPEC demonstrated 5-year survival rate from 11% to 27% [5, 52–55].

At our institution we very selectively evaluate patients with gastric cancer and PC for CRS and HIPEC. We use the PCI, determined usually by laparoscopy, and prefer the PCI be less than 10 to consider CRS and HIPEC for patients with GC. There is a role for systemic therapy prior to CRS and HIPEC for these patients and at least disease stability without progression while on chemotherapy should be a prerequisite for consideration of CRS and HIPEC. We advise that these patients only be considered and evaluated at high-volume centers that have a demonstrated experience with complex CRS and HIPEC.

Table 23.8 Studies of prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer

Reference	Type of study	Drug used	Survival (HIPEC vs no HIPEC)	Peritoneal recurrence (HIPEC vs no HIPEC)
Koga et al. [45]	Randomized controlled trial (RCT)	Mitomycin C (MMC)	30 mo: 83% vs 67%	N/A
Hamazoe et al. [46]	RCT	MMC	5 year: 64% vs 52% Median survival: 77 mo vs 66 mo	39% vs 59%
Fujimura et al. [36]	RCT	MMC and cisplatin	3 year: 68% vs 23%	9% vs 22%
Ikeguchi et al. [47]	RCT	MMC	5 year: 51% vs 46%	35% vs 40%
Fujimoto et al. [48]	RCT	MMC	2 year: 88% vs 77% 4 year: 76% vs 58% 8 year: 62% vs 49%	1.4% vs 23%
Hirose et al. [49]	Prospective case control	MMC, cisplatin, and etoposide	3 year: 49% vs 29% 5 year: 39% vs 17% Median survival: 33 mo vs 22 mo	26 vs 45%
Yonemura et al. [50]	RCT	MMC and cisplatin	5 year: 61% vs 42%	13 vs 15%
Kim et al. [51]	Prospective controlled study	MMC	5 year: 33% vs 27%	7.6% vs 25%

Modified from Seshadri and Glehen [40]

Colorectal Cancer

Patients who present with metastatic disease have 5–7% incidence of PC with one-third of those presenting with isolated PC [2]. The presence of PC worsens prognosis. Historically, the prognosis was no greater than 6 months if no intervention was undertaken [2]. The most common systemic chemotherapeutic regimens employed include leucovorin/5-fluorouracil/oxaliplatin (FOLFOX) or leucovorin/5-fluorouracil/irinotecan (FOLFIRI). The North American N9741 and N9841 trials demonstrated a median survival of 12.7 months for patients with PC and 17.6 months for patients without PC [2]. The 5-year survival rate was 4.1% and 6% for the groups [2]. The addition of newer agents bevacizumab and cetuximab has demonstrated additional survival. Median survival has been prolonged 3–6 months [2]. Saltz et al. reported a median survival of patients receiving FOLFOX + bevacizumab was 21.3 months [2, 56].

Peritoneal dissemination treated with surgery alone has demonstrated no survival benefit if complete cytoreduction cannot be carried out [2]. Studies demonstrated that median survival of patients who underwent incomplete resection ranges from 6.3 to 15months, while patients who had systemic chemotherapy alone had a mean survival of 8–17 months [2].

When the disease is limited, complete cytoreduction is feasible. Prior to the use of HIPEC, patients who had a good performance status with limited disease demonstrated a median survival of 25 months and a 5-year survival of 22% when complete cytoreduction could be performed [57]. In the same study, median survival for patients after systemic chemotherapy alone was 18 months [57]. It is generally agreed upon that a PCI <20 is possibly amenable to surgical resection. When a patient presents with a PCI >20, palliative surgery may be considered only to relieve symptoms [11, 12].

When performed at an experienced center, the 5-year survival rate for those patients who received CRS + HIPEC was 42–51% with a median survival of 33–41 months. This is compared to 13% for those who received only chemotherapy [2]. Additional studies show that after 5 years (from the date of their last treatment) 16% of patients had no recurrence and were considered "cured" [2]. However, the new novel targeted agents have allowed patients with peritoneal carcinomatosis from colorectal cancer to achieve a median survival in some cases up to 30 months with combination systemic therapy alone.

Both mitomycin C and oxaliplatin have been investigated for use during HIPEC for PC due to colorectal carcinomatosis [38]. Oxaliplatin used in short durations (30 minutes) at high concentrations appears to be well tolerated; systemic intravenous 5-fluorouracil and leucovorin are concurrently administered to enhance oxaliplatin activity [38]. Although with good initial results, recent data suggests that mitomycin C may be a better agent for HIPEC due to colorectal carcinoma with PC [58]. This was demonstrated in patients with low burden of disease and favorable pathology. Interestingly, in patients with unfavorable histology and a high burden of disease, a nonsignificant better overall survival was demonstrated when oxaliplatin was used [29]. More prospective studies are needed. There are a few studies demonstrating use of irinotecan for HIPEC [38]. This drug, which is activated through liver metabolization, has demonstrated high intraperitoneal concentrations suggesting possible activity against PC [38].

However, studies that employed irinotecan with oxalplatin demonstrated increased morbidity without survival

advantages [38]. Additional studies are needed before regular use of irinotecan. Melphalan has significant effect against a wide range of gastrointestinal malignancies [38]. Its synergist effect with heat and favorable tissue distribution makes it a good option for recurrent malignancies or salvage procedures [38].

Perhaps the most exciting change that has occurred in recent months is the addition of CRS and HIPEC into the National Comprehensive Cancer Network (NCCN) guidelines. Specifically, the Version 2.2017 guidelines suggest that for patients with synchronous abdominal/peritoneal metastases, "complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for select patients with limited PC for whom R0 resection can be achieved" [59]. This is the first mention of CRS and HIPEC in the NCCN guidelines and evidence that this may be a viable option accepted by the medical community for patients with PC from CRC.

Mesothelioma

Malignant peritoneal mesothelioma (MPM) accounts for 30% of all malignant mesothelioma cases [2, 60, 61]. It is an aggressive tumor that has dismal survival of 6–12 months without intervention [61]. Other sites for malignant mesothelioma include the pleura (most common), the pericardium, and the tunica vaginalis, with each site demonstrating individual epidemiology [2]. MPM is most common in females with a mean age of 65–66 years [2, 61].

It is suggested that the development of peritoneal mesothelioma possibly occurs through exposure to asbestos. Asbestos fibers trigger a foreign body reaction with subsequent inflammatory response. The ferritin heavy chain present in the asbestos fibers creates reactive oxygen species and reactive nitrogen species. The accumulation of these actions results in genetic disruption leading to mutations in the tumor suppressor gene *BAP-1* [60]. The asbestos is inhaled, expectorated, and swallowed. In cases without asbestos exposure, an oncogenic virus (i.e., the simian vacuolating virus—SV40) has been implicated, although more data is needed to affirm any relationship [2].

MPM is a locoregional disease, meaning it has a tendency to remain in the abdomen throughout disease progression [60, 61]. It has a highly variable rate of progression [60]. When disease is found outside of the abdomen it is most often by direct extension, trans-diaphragmatic lymphatic, or extra-abdominal lymph node metastasis [61].

Three histologic subtypes of MPM exist: epitheliod (multicystic subtype), sarcomatoid, and mixed/biphasic type. Epitheliod is the most common. Only with the use of immunohistochemical antibodies can the three types be differentiated [60]. Calretinin, cytokeratin 5/6, and vimentin are most commonly used [60]. At least two stains must be used to confirm MPM. Some studies suggest an elevated CA-125 tumor marker; however, this is unreliable and best used to monitor for recurrent disease [2, 60].

Table 23.9 A proposed staging system for malignant peritoneal mesothelioma (MPM)

Stage	Peritoneal carcinomatosis index (stratified into quartiles as a surrogate for tumor stages)	Tumor stage	Node stage (extra-abdominal nodal metastases)	Metastasis stage (extra-abdominal metastases)
I	1–10	1	0	0
II	11–20	2	0	0
	21–30	3	0	0
III	21–39	4	0–1	0–1
	1–39	1–4	1	1

Modified from Alexander Jr and Burke [60]

Staging of MPM cannot be carried out by conventional tumor-node-metastasis (TNM) staging due to its propensity to remain intra-abdominal. A proposed staging system is outlined in Table 23.9 [2, 60].

The best observed outcomes are for those with CCR 0-1. Median overall survival ranges from 30 to 92 months and was associated with epithelioid type (multicystic subvariant) absence of lymph node metastasis, achievement of CCR 0/1, and use of HIPEC [2, 60, 61]. The 1-, 3-, and 5-year survival rates after CRS with HIPEC are 70%, 60%, and 41–64% [2, 60, 61]. Age also affects survival, with a 5-year survival of 89% for those younger than 55 years versus 15% for those 55 years of age or older [61]. Features most predictive of poor prognosis include sarcomatoid growth pattern, degree of tissue invasion into stroma, fat or adjacent structures, and CCR of 2 or greater [61].

There are multiple chemotherapeutic agents reported to be effective against MPM. These include cisplatin, doxorubicin, mitomycin C, and docetaxel [2, 38]. These drugs have been used as solo regimens or in combination. The most common being cisplatin, doxorubicin, and mitomycin C. Doxorubicin has multiple features making it a good choice for HIPEC: high molecular weight, no dose-limiting toxicity (when used intraperitoneal), tumor sequestration, and thermal enhancement [38]. A point to highlight is the tumor sequestration feature of this drug. Doxorubicin will preferentially infiltrate tumor cells, despite underlying pathology [38]. It makes predicting intra-tumor concentration based on sample of peritoneal fluid difficult; however, this may result in improved efficacy of intraperitoneal administration [38]. More research is needed to discover the mechanism. The other commonly used drugs, cisplatin and mitomycin C, have been discussed elsewhere. Pemetrexed is another drug being studied for user in MPM. Pemetrexed has excellent systemic activity against mesothelioma and may be a poten-

tial agent [38]. Currently, there is no evidence suggesting a survival advantage with use of any specific drug.

Ovarian Cancer

Ovarian cancer of epithelial origin (EOC) has a worldwide incidence of more than 200,000 per year and is responsible for 125,000 deaths annually [2]. Five-year survival is less than 50% for most who present with disease that has already spread outside of the pelvis (50.2% classified as Stage III disease by The International Federation of Gynecology and Obstetrics) [2]. Approximately 13% present with distant metastasis (Stage IV).

EOC remains confined to the peritoneal cavity and retroperitoneal lymph nodes for most of its disease course [2]. For many years it was thought to arise from epithelial covering of the ovarian. However, it is now thought to more likely arise from the distal fallopian tube epithelium that adheres to the ovary during ovulation [62]. Survival for EOC is poor with a 5-year survival rate of approximately 49% [2].

A distinct subtype of EOC is low malignant potential (LMP) tumors. Often referred to as borderline or atypical tumors, LMP tumors occur at an earlier stage, younger age with a better prognosis, and less aggressive histology [2]. Peritoneal carcinomatosis is a feature of advanced disease and is associated with a poorer prognosis [2].

Broadly, the natural history of EOC can be divided according to treatment time points: front-line, front-line failure, consolidation, and recurrent disease [2]. Front-line failure is considered persistent disease at the end of front-line treatment [2]. In contrast, consolidation treatment is given following a complete response to front-line therapy [2]. Prognosis is determined by response to a platinum-based chemotherapy: platinum sensitive or platinum resistant [2]. Those with disease that recurs greater than 6 months after platinum therapy are considered sensitive, while those who recur less than 6 months are considered resistant [2].

Front-line treatment consists of CRS with platinum- and taxane-based systemic chemotherapy [2]. Prognosis is determined by the amount of residual disease after CRS, with most gynecologic oncology surgeons aiming to remove all visible disease (<1 cm) [2]. Some argue that there may be a greater chance for complete CRS if chemotherapy is administered and used to decrease the volume of disease and ascites [2]. This may improve preoperative performance status (PS), shorten the length of operation, and decrease operative morbidity [2]. Some studies demonstrated a survival advantage for patients who underwent initial CRS followed by chemotherapy (versus initial neoadjuvant chemotherapy), while a European study showed similar survival for women with Stage IIIC and IV disease [2, 63, 64]. Patients who had suboptimal CRS (>2 cm residual disease) had shorter progression-free survival (PFS) and overall survival (OS) after delivery of a platinum- and taxane-based chemotherapy versus those who had optimal CRS (<1 cm residual disease) [2]. Those with suboptimal CRS had PFS of 14.1 months and OS of 26.3 months, while those with optimal CRS had PFS of 18.3–23.8 months and OS of 48.7–65.6 months [2]. Studies have suggestive that survival may be up to 106 months if no visible disease remains at the end of CRS [2]. The addition of bevacizumab to standard chemotherapeutic regimens, for front-line treatment, has shown no significant increases in PFS or OS [2].

Prior to 2010 there were no consensus guidelines on the use of HIPEC as treatment for front-line, front-line failure, consolidation, or recurrent disease [2]. The creation of the Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer Registry (HYPERO) has allowed the pooling of data and publication of multi-institutional studies on the use of CRS + HIPEC in ovarian cancer [65–67]. The initial report from HYPERO in 2010 demonstrated no OS and 2 year PFS with use of HIPCE versus conventional treatment [2, 66, 67]. More recent data published demonstrates median OS of 25.7–30.3 months with 2-, 5-, and 10-year OS of 49.1%, 23–25.4%, and 14.3% in both treatment naïve and recurrent EOC [68, 69]. Factors significant for increased survival were sensitivity to platinum response, completeness of CCR, carboplatin alone or a combination of two or more chemotherapy agents used and duration of hospital stays of 10 days or less, Eastern Cooperative Oncology Group performance status, and preoperative serum and albumin [68, 69].

Postoperative Course, Complications, and Long-Term Surveillance

Previously diagnosed comorbidities are present in 18% of patients undergoing major oncologic resection. These morbidities increase the risk of acute medical complications (odds ratio 3.7), in-hospital mortality (OR 3.6), hospital costs, postoperative complications (OR 3.9), and increased complication severity (OR 3.6) [8]. The risk of 30-day postoperative mortality increased with increasing age, American Society of Anesthesiologists (ASA) score >3, presence of pulmonary disease, serum albumin <2.5 mg/dL and receiving >1 unit red blood cell transfusion intraoperative, liver disease, renal disease, sepsis, steroid use, weight loss, bleeding disorder, obesity, cardiac morbidity, and do not resuscitate status [70, 71]. Risk factors of increased length of stay include age >75 years, male gender, current smoker, dependent functional capacity, preoperative serum sodium <135 mmol/L, serum albumin <2.5 mg/dL, white blood cell count >11,000 cells/mm^3, and hematocrit <37% [71].

Once thought to be an extremely morbid procedure with high mortality, the consensus guidelines published by the American Society of Peritoneal Surface Malignancies has helped improve

perioperative morbidity and mortality [72]. Perioperative morbidity has been classified according to the Clavien-Dindo scale in some accounts, and this data demonstrates grade III complication rates occurring in 26–33% of cases and grade IV complications occurring in 12–26% of cases [18–20]. Average length of operation ranged from 433 to 470 minutes [18–20]. Recent data demonstrated a low morbidity and zero mortality rate for complex oncologic resections: grade I, 7%; grade II, 33%; grade III, 9%; and grade IV, 2% [73]. There was 0% mortality at 0, 30, 60, and 90 days postoperatively ($n = 54$) [73]. Length of stay was 8.2 days with 30-day readmission rate of 6% [73].

Postoperative surveillance is difficult and thus there is no consensus on optimal surveillance methods. The use of serial tumor markers is difficult; one study suggested that if preoperative CEA and CA19-9 are elevated, then an elevated postoperative CA19-9 was predictive of recurrence [74]. This does not predict the volume of disease, disease stabilization, full or partial responses [75]. Magnetic resonance imagining can detect tumor recurrence earlier than tumor markers for appendiceal neoplasms [76]. Postoperatively, patients underwent surveillance MRI and tumor markers every 6 months; recurrence was identified on average 13 months postoperatively [76]. Of the patients identified by MRI, 37% were identified to have normal tumor marker levels [76]. Tumor markers identified half as many patients with disease recurrence compared to MRI [76]. More studies are needed to evaluate imaging modalities for other pathologies. Generally, imaging should be performed at 3, 6, and 12 months postoperatively and yearly after that.

There is some data supporting the practice of a second look operation with patients who have undergone complete CRS + HIPEC with CRC and high-risk features [2]. Elias and colleagues carried out a prospective study to analyze outcomes of a second-look laparotomy 1 year after initial CRS + HIPEC [4]. All patients included in this group were found to have high-risk features at the original operation: previous-limited PC, resected ovarian metastases, and a perforated primary lesion [4]. Patients were asymptomatic and without evidence of disease (tumor markers, clinical exam, MRI, CT, PET scan) [4]. When the second look laparotomy was performed, 55% of patients were found to have visible PC [4]. These patients underwent CRS + HIPEC, and 12 months from the second look operation 50% were found to be disease free [4]. Although more trials and data are needed, this demonstrates that a planned second look laparotomy with intent for complete CRS + HIPEC may be of some benefit to select patients.

Long-term quality of life (QoL) and recovery remains largely unknown in this patient population. Traditionally associated with significant morbidity, studies now demonstrate lower morbidity rates, which may translate into improved quality of life for patients. There are few studies that explore the QoL in the postoperative period. The majority of these studies are single-center reviews that use validated questionnaires not specific for CRS + HIPEC [77]. When administered at the time of surgery and 3, 6, 9, or 12 months postoperatively, most patients demonstrate a return to an acceptable performance status between 3 and 24 month, with a return to baseline at 6–24 months postoperatively [77]. Studies demonstrate a lag in recovery of mental health while social functioning returned to baseline status 3 months postoperatively [77]. With such quick returns to an acceptable PS, one may extrapolate that patients may continue to improve beyond baseline at 6, 9, or 12 months postoperatively [77].

Conclusion

In this chapter we have attempted to give a summary of the diagnosis, management, and treatment of peritoneal malignancies. This is a rapidly evolving area of interest for surgical and medical oncologists throughout the world. Rigorous patient evaluation and selection we feel is a key to successful management of patients with PC from any malignancy. The disease burden and the histology of the primary tumor and metastases we propose are of extreme importance in determining whether patients are candidates for this approach. Finally, the performance status and lack of extra-abdominal disease are of utmost importance in evaluating this group of patients for CRS and HIPEC.

In patients with PC from appendiceal, colorectal, mesothelioma, ovarian, and primary peritoneal cancer there is a substantial amount of data and support for at least an evaluation of these patients in a center with an experienced peritoneal surface malignancy team. For other primary gastrointestinal cancers—such as gastric, pancreatic, hepatobiliary, and other more uncommon disease—there is less data to support the routine use of CRS and HIPEC. In particular, these patients should be evaluated in centers with a multidisciplinary team that has significant experience.

There continues to be new developments in this field, and it would seem the role of heated and even normothermic intraperitoneal chemotherapy for patients with PC will continue to evolve in an effort to improve the quality of life and survival of these patients faced with an extremely challenging disease.

References

1. Zhu Y, Hanna N, Boutros C, Alexander HR Jr. Assessment of clinical benefit and quality of life in patients undergoing cytoreduction and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for management of peritoneal metastases. J Gastrointest Oncol. 2013;4(1):62–71.
2. Esquivel J. Surgical oncology clinics of North America: treatment of peritoneal malignancies. Surg Oncol Clin North Am. 2012;21:4.

3. Kuijpers AM, Mirck B, Aalbers AG, Nienhuijs SW, de Hingh IH, Wiezer MJ, et al. Cytoreduction and HIPEC in the Netherlands: nationwide long-term outcome following the Dutch protocol. Ann Surg Oncol. 2013;20(13):4224–30.
4. Elias D, Goéré D, Di Pietrantonio D, Boige V, Malka D, Kohneh-Shahri N, et al. Results of a systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2008;247(3):445–50.
5. Glehen O, Schreiber V, Cotte E, Sayag-Beaujard AC, Osinsky D, Freyer G, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. Arch Surg. 2004;139:20–6.
6. Sugarbaker PH. Management of peritoneal surface malignancy using intraperitoneal chemotherapy and cytoreductive surgery: manual for physicians and nurses. Grand Rapids: The Ludann Company; 1998.
7. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.
8. Sinha P, Kallogjeri D, Piccirillo JF. Assessment of comorbidities in surgical oncology outcomes. J Surg Oncol. 2014;110(5):629–35.
9. Ford J, Coughlin KR, Van Dorp D, Berri RN. Validation of the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) risk calculator to estimate serious complications in major gastrointestinal oncologic resection. J Am Coll Surg. 2015;221(4 Suppl. 2):e135–6.
10. Valle M, Federici O, Garofalo A. Patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, and role of laparoscopy in diagnosis, staging and treatment. Surg Oncol Clin N Am. 2012;21(4):515–31.
11. Harmon RL, Sugarbaker PH. Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. Int Semin Surg Oncol. 2005;2(1):3.
12. Pelz JO, Stojadinovic A, Nissan A, Hohenberger W, Esquivel J. Evaluation of a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol. 2009;99(1):9–15.
13. Keating NL, Landrum MB, Lamont EB, Bozeman SR, Shulman LN, McNeil BJ. Tumor boards and the quality of cancer care. J Natl Cancer Inst. 2013;105(2):113–21.
14. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010;28(1):63–8.
15. Sugarbaker PH. Management of peritoneal surface malignancy: the surgeons role. Langenbacks Arch Surg. 1999;384:576–87.
16. Yoon W, Alame A, Berri R. Peritoneal surface disease severity score as predictor of resectability in treatment of peritoneal surface malignancies. Am J Surg. 2014;207(3):403–7; discussion 406–7.
17. Esquivel J, et al. ASPSM multi-institution evaluation of the peritoneal surface disease severity score in 1,013 patients with colorectal cancer with peritoneal carcinomatosis. Ann Surg Oncol. 2014;21:4195–201.
18. Tsilimparis N, Bockelmann C, Raue W, Menenakos C, Perez S, Rau B, et al. Quality of life in patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: is it worth the risk? Ann Surg Oncol. 2013;20(1):226–32.
19. Tan WJ, Wong JF, Chia CS, Tan GH, Soo KC, Teo MC. Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: an Asian perspective. Ann Surg Oncol. 2013;20(13):4219–23.
20. Glockzin G, Schlitt HJ, Piso P. Peritoneal carcinomatosis: patients selection, perioperative complications and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg Oncol. 2009;7:5.
21. Esquivel J, Angulo F, Bland RK, Stephens AD, Sugarbaker PH. Hemodynamic and cardiac function parameters during heated intraoperative intraperitoneal chemotherapy using the open "coliseum technique". Ann Surg Oncol. 2000;7(4):296–300.
22. Turaga K, Levine E, Barone R, Sticca R, Petrelli N, Lambert L, et al. Consensus guidelines from the American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. Ann Surg Oncol. 2014;21:1501–5.
23. Joshi GP. Intraoperative fluid restriction improves outcomes after major electives gastrointestinal surgery. Anesth Analg. 2005;101(2):601–5.
24. Bailey JM. Dopamine: one size does not fit all. Anesthesiology. 2000;92(2):303–5.
25. Thix CA, Königsrainer I, Kind R, Wied P, Schroeder TH. Ventricular tachycardia during hyperthermic intraperitoneal chemotherapy. Anesethsia. 2009;64(10):1134–6.
26. Rueth NM, Murray SE, Huddleston SJ, Abbott AM, Greeno EW, Kirstein MN, et al. Severe electrolyte disturbances after hyperthermic intraperitoneal chemotherapy: oxaliplatin versus mitomycin C. Ann Surg Onc. 2011;18(1):174–80.
27. Esquivel J, Averbach A, Chua T. Laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with limited peritoneal surface malignancies: feasibility, morbidity and outcome in an early experience. Ann Surg. 2011;253(4):764–8.
28. Passot G, Bakrin N, Isaac S. Postoperative outcomes of laparoscopic vs open cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for treatment of peritoneal surface malignancies. Eur J Surg Oncol. 2014;40(8):957–62.
29. Sugarbaker PH. Cytoreductive surgery using peritonectomy and visceral resections for peritoneal surface malignancy. Transl Gastrointest Cancer. 2013;2(2)
30. Bijelic L, Sugarbaker PH. Cytoreduction of the small bowel surfaces. J Surg Oncol. 2008;97(2):176–9.
31. Halkia E, Efstathiou E, Rogdakis A, Christakis C, Spiliotis J. Digestive fistulas after cytoreductive surgery & HIPEC in peritoneal carcinomatosis. J BUON. 2015;20(Suppl 1):S60–3.
32. Esquis P, Consolo D, Magnin G, Pointaire P, Moretto P, Ynsa MD, et al. High intraabdominal pressure enhances the penetration and antitumor effect of intraperitoneal cisplatin on experimental peritoneal carcinomatosis. Ann Surg. 2006;244(1):106–12.
33. Esquivel J. Membership. http://www.americansocietypsm.org. Last accessed May 15, 2018.
34. González-Moreno S, González-Bayón LA, Ortega-Pérez G. Hyperthermic intraperitoneal chemotherapy: rationale and technique. World J Gastrointest Oncol. 2010;2(2):68–75.
35. Esquivel J, Sugarbaker PH, Helm CW. Techniques of delivering hyperthermic intraperitoneal chemotherapy. In: Helm CW, Edwards RP, editors. Intraperitoneal Cancer therapy. Current clinical oncology: Springer; 2007.
36. Fujimura T, Yonemura Y, Muraoka K, Takamura H, Hirono Y, Sahara H, et al. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. World J Surg. 1994;18(1):150–5.
37. Glehen O, Cotte E, Kusamura S, Deraco M, Baratti D, Passot G, et al. Hyperthermic intraperitoneal chemotherapy: nomenclature and modalities of perfusion. J Surg Oncol. 2008;98:242–6.
38. De Bree E. Optimal drugs for HIPEC in different tumors. J BUON. 2015;20(Suppl. 1):S40–6.
39. Sugarbaker PH. When and when not to perform a right colon resection with mucinous appendiceal neoplasms. Ann Surg Oncol. 2017;24(3):729–32.
40. Seshadri R, Glehen O. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer. World J Gastroenterol. 2016;22(3):1114–30.

41. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, Japan Clinical Oncology Group, et al. D2 lymphadenectomy alone or with paraaortic nodal dissection for gastric cancer. N Engl J Med. 2008;359(5):453–62.
42. D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg. 2004;240(5):808–16.
43. Yu XF, Ren ZG, Xue YW, Song HT, Wei YZ, Li CM. D2 lymphadenectomy can disseminate tumor cells into peritoneal cavity in patients with advanced gastric cancer. Neoplasma. 2013;60:174–81.
44. Sugarbaker PH, Yu W, Yonemura Y. Gastrectomy, peritonectomy and perioperative intraperitoneal chemotherapy: the evolution of treatment strategies for advanced gastric cancer. Semin Surg Oncol. 2003;21:233–48.
45. Koga S, Hamazoe R, Maeta M, Shimizu N, Murakami A, Wakatsuki T. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. Cancer. 1988;61:223–37.
46. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrences of gastric cancer. Final results of a randomized controlled study. Cancer. 1994;73:2048–52.
47. Ikeguchi M, Kondou A, Oka A, Tsujitani S, Maeta M, Kaibara N. Effects of continuous hyperthermic peritoneal perfusion on prognosis of gastric cancer with serosal invasion. Eur J Surg. 1995;161:581–6.
48. Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrences in patients with advanced gastric cancer. Cancer. 1999;85:529–34.
49. Hirose K, Katayama K, Iida A, Yamaguchi A, Nakagawara G, Umeda S, et al. Efficacy of continuous hyperthermic peritoneal perfusion for the prophylaxis and treatment of peritoneal metastasis of advanced gastric cancer; evaluation by multivariate regression analysis. Oncology. 1999;57:106–14.
50. Yonemura Y, de Aretxabala X, Fujimura T, Fushida S, Katayama K, Bandou E, et al. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study. Hepato-Gastroenterology. 2001;48:1776–82.
51. Kim JY, Bae HS. A controlled clinical study of serosa-invasive gastric carcinoma patients who underwent surgery plus intraperitoneal hyperthermo-chemo-perfusion (IHCP). Gastric Cancer. 2001;4(1):27–33.
52. Yonemura Y, Fujimura T, Nishimura G, Falla R, Sawa T, Katayama K, et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. Surgery. 1996;119:437–44.
53. Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T, Isawa E, et al. Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. Cancer. 1997;79(5):884–91.
54. Yonemura Y, Kawamura T, Bandou E, Takahashi S, Sawa T, Matsuki N. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Br J Surg. 2005;92:370–5.
55. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, et al. Peritoneal carcinomatosis from gastric cancer: a multiinstitutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Am Surg Oncol. 2010;17:2370–7.
56. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as a first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:1013–9.
57. Mulsow J, Merkel S, Agaimy A, Hohenberger W. Outcomes following surgery for colorectal cancer with synchronous peritoneal metastases. Br J Surg. 2011;98:1785–91.
58. Prada-Villaverde A, Esquivel J, Lowy AM, Markman M, Chua T, Pelz J, et al. American Society of Peritoneal Surface Malignancies evaluation of HIPEC with mitomycin C versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. J Surg Oncol. 2014;110:779–85.
59. National Comprehensive Cancer Network. NCCN Guidelines® & Clinical Resources. https://www.nccn.org/professionals/physician_gls/default.aspx. Last accessed May 16, 2018.
60. Alexander HR Jr, Burke AP. Diagnosis and management of patients with malignant peritoneal mesothelioma. J Gastrointest Oncol. 2016;7(1):79–86.
61. Magge D, Zenati MS, Austin F, Mavanur A, Sathaiah M, Ramalingam L, et al. Malignant peritoneal mesothelioma: prognostic factors and oncologic outcome analysis. Ann Surg Oncol. 2014;21:1159–65.
62. Kurman RJ, Shih LM. Molecular pathogenesis and extraovarian origin of ovarian cancer – shifting the paradigm. Hum Path. 2011;42:918–31.
63. Bristow RE, Eisenhauer EL, Santillan A, Chi DS. Delaying the primary surgical effort for advanced ovarian cancer: a systematic review of neoadjuvant chemotherapy and interval cytoreduction. Gynecol Oncol. 2007;104:480–90.
64. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group, NCIC Clinical Trials Group, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363:943–53.
65. Karadayi K, Yildiz C, Karakus S, Akkar OB, Ugurlu GP, Kurt A, et al. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for gynecologic malignancies: a single center experience. Eur J Gynaecol Oncol. 2016;37(2):194–8.
66. Jaaback K, Johnson N. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancers. Cochrane Database Syst Rev. 2006;1:CD005340.
67. Helm CW, Richard SD, Pan J, Bartlett D, Goodman MD, Hoefer R, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer: first report of the HYPER-O registry. Int J Gynecol Cancer. 2010;20(1):61–9.
68. Deraco M, Virzì S, Iusco DR, Puccio F, Macrì A, Famulari C, et al. Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multiinstitutional study. BJOG. 2012;119(7):800–9.
69. Deraco M, Kusamura S, Virzì S, Puccio F, Macrì A, Famulari C, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: multi-institutional phase-II trial. Gynecol Oncol. 2011;122(2):215–20.
70. Vaid S, Bell T, Grim R, Ahuja V. Predicting risk of death in general surgery patients on the basis of preoperative variables using American College of Surgeons Quality Improvement Program data. Perm J. 2012;16(4):10–7.
71. Borja-Cacho D, Parsons HM, Habermann EB, Rothenberger DA, Henderson WG, Al-Refaie WB. Assessment of ACS NSQIP/s predictive ability for adverse events after major cancer surgery. Ann Surg Oncol. 2010;17(9):2274–82.
72. Turaga K, Levine E, Barone R, Sticca R, Petrelli N, Lambert L, et al. Consensus guidelines from the American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. Ann Surg Oncol. 2014;21(5):1501–5.

73. Van Dorp DR, Boston A, Berri RN. Establishing a complex surgical oncology program with low morbidity and mortality at a community hospital. Am J Surg. 2015;209(3):536–41.
74. Low R. Preoperative and surveillance MR imaging of patients undergoing cytoreductive surgery and heated intraperitoneal chemotherapy. J Gastrointest Oncol. 2016;7(1):58–71.
75. Jacquet P, Sugarbaker P. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–74.
76. Low RN, Barone RM, Lee MJ. Surveillance MR imaging is superior to serum tumor markers for detecting early tumor recurrence in patients with appendiceal cancer treated with surgical cytoreduction and HIPEC. Ann Surg Oncol. 2013;20:1074–81.
77. Ford J, Hanna M, Boston A, Berri R. Life after hyperthermic intraperitoneal chemotherapy; measuring quality of life and performance status after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. Am J Surg. 2016;211(3):546–50.

Advances in Radiation Therapy for Gastrointestinal Cancers

24

Rachit Kumar, Lauren M. Rosati, and Joseph M. Herman

Introduction

The role of radiation therapy (RT) in the treatment of gastrointestinal (GI) malignancies has been well established; however, the optimal radiation technique and timing of radiation are less clear. The past decade has contributed immensely to the advances in treatment planning and delivery as improved imaging and technology have surfaced. It is now possible to precisely deliver high doses of radiation while sparing nearby critical organs. Standard of care has transitioned from three-dimensional conformal radiation therapy (3D-CRT) to intensity-modulated radiation therapy (IMRT), and image guidance has become widely adopted worldwide. Stereotactic body radiation therapy (SBRT) has recently emerged as a viable, if not more effective, alternative to safely provide local control (LC) with millimeter accuracy.

Novel imaging techniques using computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) have contributed to increased accuracy in treatment setup, target delineation, and evaluation of tumor response following therapy. Techniques such as four-dimensional CT (4DCT) imaging and motion management now allow for ablative doses to be achieved with limited treatment-related toxicity. Nonetheless, a considerable number of management questions remain unanswered as we continue to investigate options for these high-risk patients given a poor prognosis. In combination with interventional radiology and surgery, radiation therapy plays a large role in maximizing local control; however, distant control and tumor progression remain a large concern in these aggressive GI malignancies. As the field of radiation oncology advances, there is a need for improved systemic and targeted therapies in order to achieve optimal multidisciplinary care. The discovery of novel biomarkers, prediction of radiosensitivity, and response to therapy should result in more patients receiving personalized therapy.

Modern Methods of Radiation Delivery

Intensity-Modulated Radiation Therapy

While radiation therapy was once delivered only using radioactive sources (including within linear accelerators [linacs]), modern forms of radiation therapy are generated from an electrical current by speeding charged particles (electrons) to velocities approaching the speed of light. While an in-depth assessment of the physics behind this process is beyond the scope of this chapter, this development drastically moved the field of radiation away from dependence on acquiring and generating radioactive sources as the basis of all radiotherapy.

For decades, radiation therapy was delivered to patients using beams aimed at a center point (isocenter) within the patient; however, this delivery was limited by the lack of ability to model radiation dose distribution more precisely, and practitioners often relied on surrogate markers for radiation dose including skin erythema. Consequently, radiation doses were delivered to a maximum tolerable dose based on a general understanding of normal tissue dose constraints. In his

R. Kumar
Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

University of Arizona, College of Medicine – Phoenix, Tucson, AZ, USA

Banner Thunderbird Medical Center, Glendale, AZ, USA

Banner MD Anderson Cancer Center, Gilbert, AZ, USA

L. M. Rosati
Department of Radiation Oncology & Molecular Radiation Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

J. M. Herman (✉)
Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Department of Radiation Oncology & Molecular Radiation Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: JMHerman@mdanderson.org

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_24

landmark paper, Emami published the first set of comprehensive formalized dose constraints in the field of radiation oncology [1]. With the advent of CT-based planning, radiation oncologists were now able to more accurately deliver radiation dose to the target (tumor) while avoiding adjacent normal tissues. The combined understanding of normal tissue dose limitations and accurate modeling of internal radiation dose pushed the field of radiation to pursue methods in which higher doses of radiation would be delivered to the target while simultaneously limiting normal tissue dose.

Intensity-modulated radiation therapy (IMRT) resulted from the improvement in technology and understanding of normal tissue dose. IMRT allows radiation to be precisely "sculpted" to target the lesion and spare normal tissues around the lesion. Using tungsten metal leaves within the linac, the radiation shape can be molded to the appearance of the lesion. Additionally, the linac is composed of a table (on which the patient is lying flat) and the gantry (in which the radiation beam is generated). The gantry is able to move around the patient and deliver radiation beams from multiple angles. These beams are able to meet at a pre-defined point (the isocenter) and deposit a combined high dose of radiation at this target, whereas the surrounding tissue is avoided using established normal tissue parameters. For many tumors, the use of IMRT has become standard of care on the basis of clinical trials demonstrating excellent local tumor control and reduced acute and chronic toxicity.

Volumetric Modulated Arc Therapy

Building upon the advancements provided by IMRT, radiation oncologists and physicists investigated the combination of IMRT and arc therapy. Arc therapy is an external beam radiation therapy (EBRT) applied using a radiation beam that remains active as the gantry rotates around a patient. This is in contrast to traditional IMRT in which the gantry remains fixed at a point, delivers the radiation beam, and then moves to the next beam position for treatment delivery. Arc therapy has the benefit of providing a more homogeneous dose distribution more rapidly, thereby reducing both patient and machine time. Representative examples of rectal cancer plans using 3D conformal radiation, IMRT, and volumetric modulated arc therapy (VMAT) are shown in Fig. 24.1.

Volumetric modulated arc therapy combines the benefits of arc therapy and intensity modulation. This technique employs constant gantry movement (as opposed to fixed-beam IMRT treatment) as well as modulation of the treatment volume (shaping the beam to better conform to the patient). Dosimetric studies of VMAT compared to IMRT have been published for upper and lower GI cancers, including pancreatic, gastric, and rectal cancers [2–5]. As expected, VMAT better aligns with specific normal tissue targets and allows for complete treatment within a significantly shorter period of time. Due to the complexity of this treatment, appropriate experience on the part of dosimetrist and physicist is required to ensure adequate quality assurance prior to safe treatment delivery.

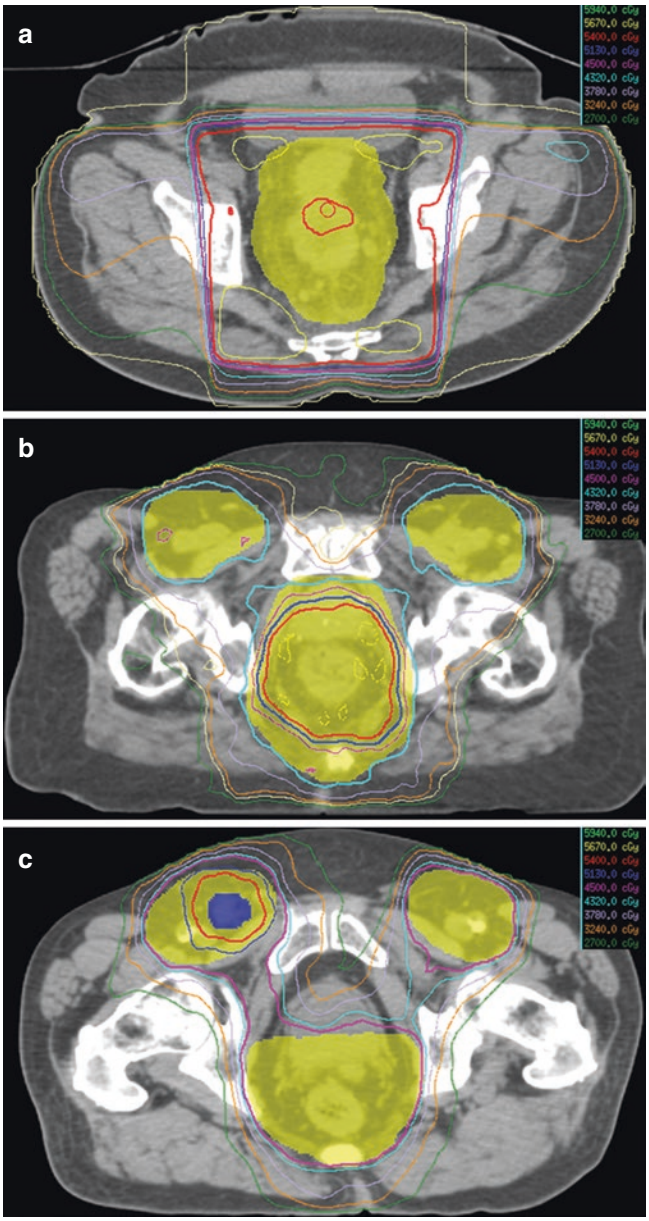


Fig. 24.1 Examples of rectal cancer plans using (**a**) 3D conformal (3D-CRT), (**b**) static-field intensity-modulated radiation therapy (IMRT), and (**c**) volumetric modulated arc therapy (VMAT) are presented. (**a**) A standard 3-field pelvis plan (right lateral, left lateral, and posteroanterior beams) results in a "box" dose distribution that treats the target volume (yellow), but with significant dose at the entry points both bilateral and posterior. (**b**) IMRT results in better dose distribution, particularly in this patient in whom the inguinal nodes are treated. However, while the dose is more conformal around the target volume in yellow, the distribution remains slightly more heterogeneous around the target. (**c**) A VMAT plan results in the most conformal dose around the yellow target volume with less high dose to uninvolved areas. However, while not appreciable on this image, low doses of radiation would be seen throughout the uninvolved soft tissue due to the 360° rotation of the linear accelerator

Stereotactic Body Radiation Therapy

While IMRT has changed the method in which radiation therapy has been delivered in recent years, SBRT, also known as stereotactic ablative body radiation (SABR), has altered the landscape of radiation in the past decade. SBRT is the use of high-dose-per-fraction radiation delivered over a short course (1–5 fractions) as opposed to standard radiation fractionation that uses lower doses per fraction delivered for 5–6 weeks.

SBRT has only recently been possible as a consequence of modern advents of radiation therapy. Previously mentioned utilization of CT simulation has allowed for more accurate modeling of radiation dose within the patient. Daily imaging, often in the form of on-board CT scanners built into the radiation treatment machine, allows for accurate visualization of the lesion within the body for more precise targeting of the lesion. Increased speed of radiation delivery reduces the amount of time that a patient is required to lay on the treatment table. The combination of the aforementioned technologies allows radiation oncologists to plan for higher doses of radiation to the tumor, a minimal treatment margin (sometimes no margin) around the lesion, accurate visualization of the lesion within the patient, and rapid dose fall-off away from the tumor. In some cases, these therapies result in outcomes that rival surgical excision [6].

These treatment approaches have both practical and clinical advantages over standard radiation therapy. From a practical perspective, decreased time receiving radiation allows for longer intervals of full-dose chemotherapy. Additionally, acute side effects are often decreased with shorter courses of more focused radiation therapy. From a clinical perspective, higher doses of radiation per delivery (daily fraction) generally results in a higher comparative radiation dose based on a radiobiological principle known as the biologically equivalent dose (BED). The BED is a method of comparing different dose fractionations to model how much radiation is being delivered with different doses per fraction and number of fractions. SBRT doses tend to result in a higher BED that may be more ablative than conventionally fractionated BED [7]. However, normal tissues are also limited by this same BED principle, as this high-dose-per-fraction radiation may lead to a higher risk of long-term normal tissue damage, potentially due to long-term vascular endothelial injury.

Heavy Particle Therapy

Heavy particle therapy is the use of charged or inert large particles that are accelerated to the speed of light to deposit energy within tissue. They have multiple theoretical advantages, some of which have been realized clinically. Whereas electron and photon irradiation have entrance and exit radiation doses, including high skin surface doses (electrons and low-energy photons), heavy particle therapy delivers lower initial doses, higher depth doses, and very little exit dose. Consequently, it presents a theoretical advantage in delivering radiation to the target and minimal damage to surrounding tissues. The most common type of heavy particle therapy is proton therapy, which has a slightly higher radiobiological effect on the tumor than standard therapy.

The largest barriers to the universal implementation of heavy particle therapy include the size of the treatment machines as well as the initial cost. Although many centers have begun utilizing heavy particle therapy for many malignancies, the data demonstrating a clinical benefit is currently being evaluated in large clinical trials [8]. In certain populations, including pediatrics, there is a general consensus among radiation oncologists of a true benefit to using heavy particle therapy [9]. However, there is a wide disagreement in its utilization for other malignancies, particularly in the elderly who are unlikely to realize the benefits of reduced normal tissue dose in the long term. Another challenge includes the inability to utilize daily image guidance in the same manner as IMRT. Data on the use of heavy particle therapy will continue to emerge as the adoption of this technology expands.

Intraoperative Radiation Therapy

Even in the hands of skilled surgeons, some oncologic surgeries cannot remove all microscopic disease. In the setting of microscopic disease infiltration, intraoperative radiation therapy (IORT) allows for sterilization of possible disease along the resection margin to reduce the risk of a local recurrence. IORT is not used in isolation; instead it is combined with either neoadjuvant or adjuvant external beam radiation therapy (EBRT) for approximately 5 weeks. At the time of surgery, a single fraction of radiation using a dose of 10–15 Gray (Gy) to the surface or 5 mm depth is applied during the surgical procedure. As the surgical field is exposed, normal tissues may be mobilized to help prevent radiation damage that would otherwise be realized with standard EBRT.

Methods of IORT include either externally applied radiation (IOERT, using EBRT to maximize surface dose) or high-dose-rate brachytherapy (HDR-IORT, designed to have a rapid dose decrease past the tissue surface). This therapy has been investigated in recurrent rectal cancer, pancreatic cancer, and sarcomas [10–13]. Meticulous attention to detail is required with this procedure given the very high doses of radiation utilized. An operating room (OR) suite that provides radiation shielding is required for physics quality assurance and safety parameters [14].

Esophageal Cancer

Radiation therapy remains an important local treatment modality in patients with esophageal cancer. While esophagectomy is considered the mainstay of therapy in patients with early stage, operable esophageal and gastroesophageal (GE) junction cancers, radiation therapy is indicated both for patients with unresectable disease and in the neoadjuvant setting prior to surgery.

To date, the superiority of chemoradiation as opposed to radiation alone has been established in non-metastatic esophageal cancer [15]. Although dose escalation with radiation has not demonstrated superiority over standard dose radiation, the benefit of dose escalation may be more realized with the improved technology outlined earlier in the chapter [16]. The outcome of the Intergroup 0123 phase III trial investigating the role of dose-escalated radiation to a dose of 64.8 Gy with concurrent chemotherapy versus a standard dose of 50 Gy with concurrent chemotherapy reported that median overall survival (OS) was greater for patients treated on the standard dose arm rather than the dose escalation arm, though not statistically significant (13.0 versus 18.1 months). While there are multiple criticisms of this trial, perhaps one of the most salient is the fact that the majority of deaths seen on this study occurred prior to reaching the dose escalation portion of the treatment. For now, a dose of 50–50.4 Gy in the definitive setting remains the standard of care, though the question of dose escalation may again be raised in future trials.

Surgical resection remains the optimal course of therapy in appropriately selected esophageal and GE junction cancer patients. At least three randomized trials have now demonstrated the superiority of neoadjuvant therapy using chemoradiation versus an upfront surgical resection. The CALGB 9781 trial randomized patients to two cycles of chemotherapy and 50.4 Gy of radiation followed by surgery versus surgery alone [17]. With a median follow-up of 6 years, there was a statistically significant improvement in both median (4.5 years in the neoadjuvant arm versus 1.8 years in the surgery alone arm) and 5-year OS (39% neoadjuvant vs. 16% surgery alone). Similar results were seen in the recently published phase III ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial by Van Hagen and colleagues [18]. In this study, patients received neoadjuvant carboplatin and paclitaxel combined with 41.4 Gy of 3D-CRT followed by surgery or upfront surgery alone. Median OS was 49 months in patients receiving neoadjuvant therapy versus 24 months in patients receiving surgery alone (hazard ratio [HR] 0.66, $p = 0.003$); 5-year OS was also improved with neoadjuvant therapy (47% versus 34%). Despite a lower dose of radiation than is typically used, the CROSS trial reduced the risk of local regional recurrence (14% versus 34%, $p > 0.001$) and peritoneal carcinomatosis (4% versus 14%, $p < 0.001$) versus surgery alone. Finally, the Preoperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma Trial (POET) investigated the role of induction chemotherapy followed by surgery versus induction chemotherapy and then chemoradiation followed by surgery in patients with locally advanced GE junction cancers [19]. Despite closing early due to poor control, the use of radiation was associated with an improved pathologic complete response and node-negative resection rate, as well as a trend toward improved 3-year OS.

In sum, radiation is effective both in the definitive setting and in the neoadjuvant setting. More recent data has emerged regarding the use of advanced radiation techniques including IMRT and charge particle therapy in the treatment of esophageal cancer.

Intensity-Modulated Radiation Therapy in Esophageal Cancer

Given the close relationship of the esophagus to multiple critical structures within the thorax and abdomen, dose escalation has been limited not only by the inherent sensitivity of the GI tract to radiation but also by the spinal cord, heart, and lungs. The potential for delivering radiation to the esophageal cancer while sparing these normal tissues has generated significant interest in the use of IMRT for this disease.

Multiple retrospective dosimetric studies have shown improvement in lung dose and cardiac dose with the use of IMRT. Data from the MD Anderson Cancer Center (MDACC) demonstrated an improvement in lung dosimetry when using IMRT [20]. Reductions were seen in clinically significant parameters including V10 (volume of lung receiving ≥ 10 Gy of radiation), V20 (volume of lung receiving ≥ 20 Gy of radiation), and mean lung dose. Researchers from Memorial Sloan Kettering Cancer Center (MSKCC) have reported the ability of IMRT to spare cardiac tissue including reductions to the cardiac V30, mean heart dose, and mean dose to the right carotid artery [21]. However, the Memorial Sloan Kettering study did not report a statistically significant reduction in lung dose.

Clinically, the MDACC team showed a reduction in weight loss with IMRT as opposed to 3D-CRT [22]. Greater than 10% body weight was lost in 23.2% of patients when treated with 3D-CRT and in only 15.6% of patients treated with IMRT ($p = 0.04$). Intriguingly, no changes were seen in the rates of feeding tube placement, esophagitis, and nausea. However, at an early follow-up interval of 34.6 months, median OS (36 months vs. 24 months) and 5-year overall OS

(42.4 vs. 31.3%) were both statistically greater in patients treated with IMRT ($p = 0.009$). No difference was seen in the rate of cancer or pulmonary deaths, but a reduction was seen in both cardiac and "other" deaths.

Based on these results, the utilization of IMRT in the treatment of esophageal cancer has been increasing. Previous Radiation Therapy Oncology Group (RTOG) trials, including RTOG 0436, have specifically stated that the use of IMRT is not allowed. However, the most recent RTOG trials, including RTOG 1010, do allow the use of IMRT as an appropriate delivery method of radiation (www.rtog.org/clinicaltrials/protocoltable.aspx). With the endorsement of the RTOG, it is reasonable to assume that many centers will adopt IMRT as a reasonable standard of care for radiation in esophageal cancer.

Charged Particle Therapy in Esophageal Cancer

With the ability of charged particle therapy to effectively deliver dose to a depth with minimal exit radiation dose, esophageal cancer is an intriguing application for this therapy to minimize dose to the heart, lungs, and spinal cord. Due to the paucity of data for dose escalation in esophageal cancer, particle therapy has typically remained limited to the setting of a boost as opposed to definitive therapy.

Data from MDACC demonstrated that an intensity-modulated proton therapy (IMPT) plan was able to reduce radiation dose to the lungs, heart, and liver, compared to an IMRT treatment plan [23]. This dosimetric analysis compared various IMRT and IMPT plans and treated the initial planning target volume (PTV) to 50.4 Gy and boosted the gross tumor volume (GTV) to 64.8 Gy using 28 fractions in a concomitant boost technique. The most optimal plan for reducing dose to these key structures was using a three-beam IMPT arrangement with anteroposterior (AP), left posterior oblique (LPO), and right posterior oblique (RPO) beams. Specifically, statistically significant reductions were seen in the mean lung (4.30 vs. 8.27 Gy, $p = 0.002$), heart (17 vs. 21.2 Gy, $p = 0.003$), and liver doses (5.4 v 14.9 Gy, $p \leq 0.0001$) when compared to the IMRT plan. Improvements were also seen in other parameters associated with long-term toxicity including the V20 to the lung (percentage, by volume, of lung receiving at least 20 Gy). A representative example of an esophageal plan with dosimetric improvement using proton therapy is seen in Fig. 24.2 [23]. Clinical data on the use of proton beam therapy has demonstrated potentially greater efficacy, with higher 5-year OS rates than with conventional radiotherapy, again using the proton beam therapy as a method to boost the primary tumor. Additionally, no grade 3 or higher cardiopulmonary toxicities were reported using this boost technique [23].

Investigators from Japan have reported results from their phase I/II clinical trials using carbon ions in a hypofractionated approach (to maximize the higher relative biological effectiveness of charged particles) [24]. In the first trial, the investigators reported one (3.2%) late grade 3 toxicity (grade 3 acute respiratory disease syndrome in a patient treated with 35.2 GyE in eight fractions over 2 weeks). In the follow-up trial using 43.2 GyE to 50.4 GyE in 12 fractions over 3 weeks, 4 cases of acute grade 3 toxicity were seen (2 cases of grade 3 acute esophagitis and 2 cases of grade 3 acute leucopenia). No cases of late grade 3 or higher toxicity were appreciated in the dose escalation trial. In both studies, the rates of complete pathologic response were significantly greater than historical controls. In the dose escalation trial, 88% of patients (14 of 16) achieved a complete response. All patients treated with a dose of 45.6 GyE or higher showed a complete response. These results hold a tremendous amount of promise, but it should be noted that these were well-selected patients with resectable tumors.

As the availability of both proton and carbon-ion radiotherapy grows, more clinical data will inevitably emerge. The potential for dose escalation using this technology is significant and should ideally prompt a randomized trial to verify the benefits purported in the discussed early phase clinical trials.

Positron Emission Tomography-Directed Therapy in Radiation Planning for Esophageal Cancer

In the 3D conformal era, the target volume for esophageal cancers has involved treating 5 cm superior/inferior and 2 cm radially from the gross target volume as identified on planning CT scans and upper endoscopy. With the increased use of IMRT, the target volume is now typically reduced to 4 cm superior/inferior and 1–1.5 cm radially. However, it is well recognized that CT scans alone are a suboptimal technique for identifying the tumor and involved lymph nodes.

The use of PET scans to help better identify gross tumor and lymph node extent has been the area of active clinical investigation. The use of PET fusion with a planning CT scan has been found to both increase and decrease the delineation of gross tumor volume compared to CT scanning alone [25]. Importantly, PET scanning has helped to identify metabolically active lymph nodes that would not otherwise meet size criteria for treatment. The identification of a standardized uptake value (SUV) threshold is important, and an SUV of 2.5 has been identified as a potential minimum value for inclusion in the treatment volume.

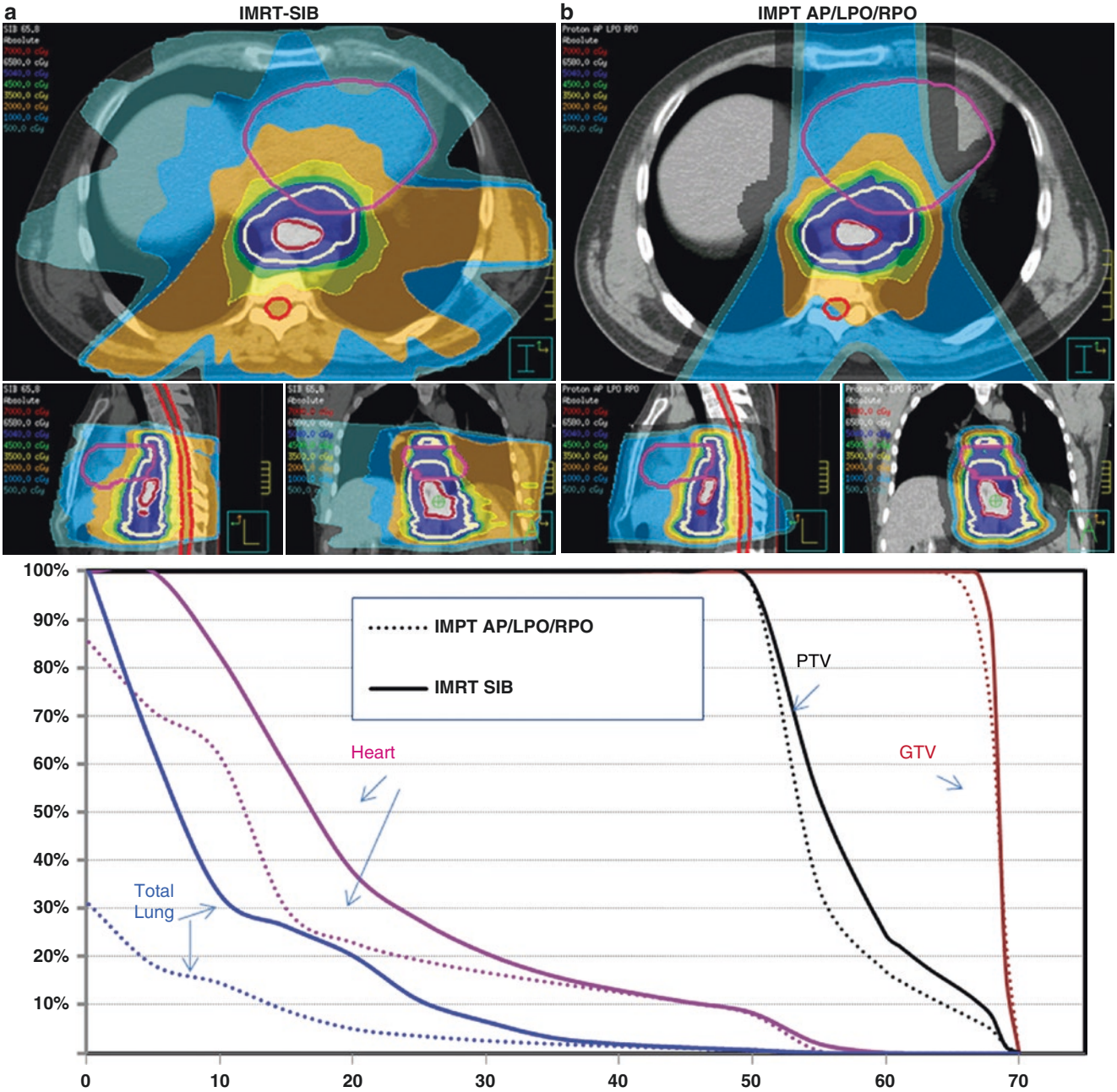


Fig. 24.2 (**a**) Axial, sagittal, and coronal views of intensity-modulated radiotherapy (IMRT) – simultaneous integrated boost (SIB) plan, with planning target volume (PTV) treated to 50.4 Gy and gross tumor volume (GTV) boosted to 65.8 Gy. (**b**) Axial, sagittal, and coronal views of intensity-modulated proton therapy (IMPT) (anteroposterior/left posterior oblique/right posterior oblique [AP/LPO/RPO]) plan, with PTV treated to 50.4 Gy and GTV boosted to 65.8 Gy. AP/LPO/RPO beam arrangement was optimal for achieving both pulmonary and cardiac sparing compared with IMRT plan. (Reprinted with permission from Welsh et al. [23])

Gastric Cancer

Surgical resection remains the optimal curative modality in patients with non-metastatic gastric adenocarcinoma. The National Comprehensive Cancer Network (NCCN) recommends a D2 resection whenever technically feasible, with a recommendation to obtain at least 15 draining lymph nodes. However, chemotherapy with or without radiation remains critical in both the perioperative and adjuvant setting. Much like the treatment of esophageal cancer, the use of radiation has been limited by the radiosensitivity of the alimentary tract. Advanced radiation techniques, including IMRT and particle therapy, have been investigated as methods to deliver

higher doses of radiation while limiting the morbidity of therapy.

The two major trials that guide perioperative and adjuvant therapy are the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial [26] and the Intergroup/Southwest Oncology Group (SWOG) 0116 trial [27], respectively. Both trials included patients with stage II–IV non-metastatic gastric and GE junction adenocarcinoma patients (though the Intergroup/SWOG trial included patients with stage IB cancers as well), and each had slightly more than 500 patients included on the studies. Each trial had a 1:1 randomization between surgery alone and either surgery alone or perioperative/adjuvant therapy. However, an important difference between the trials is that patients were enrolled after margin-negative (R0) resection in the Intergroup study and at the time of diagnosis in the MAGIC trial. For this reason alone, direct comparison between the two trials is not possible.

The MAGIC trial indicated that three cycles of perioperative ECF (epirubicin, cisplatin, and infusional 5-fluorouracil [5-FU]) chemotherapy improved survival over surgery alone (5-year OS, 36% vs. 23%, $p = 0.008$). However, no downstaging or increase in pathologic response was seen with perioperative chemotherapy, including no complete responses, no improvement in the R0 resection rate, and no difference in nodal disease. Further, only 41% of patients in the chemotherapy group completed all of the assigned chemotherapy. The Intergroup trial, as stated earlier, pre-selected for patients with an R0 resection. Following surgery, patients were assigned to no further therapy or one cycle of bolus 5-FU, followed by combined 5-FU and radiation to a dose of 45 Gy in 1.8 Gy fractions and then additional two cycles of bolus 5-FU. A statistically significant improvement in OS (35 vs. 27 months, $p = 0.0046$) and median relapse-free survival (27 vs. 19 months, $p < 0.001$) was seen with the addition of postoperative therapy. Although a D2 resection was recommended along with the gastrectomy, only 10% of patients underwent this surgery, leading to a question of whether or not radiation is compensating for inadequate surgery, as the lack of a thorough nodal resection likely contributed to the lower survival numbers in the surgery alone arm. Additionally, major deviations from the recommended RT protocol were seen in 41% of the submitted radiation therapy plans.

Based on the results of the aforementioned two trials, perioperative chemotherapy became the standard of care in Europe, while many centers in the United States adopted the postoperative chemoradiation protocol from the Intergroup/SWOG trial. More recent studies are working to refine the optimal approach from the above studies, specifically on the superiority of perioperative or adjuvant chemotherapy versus adjuvant chemoradiation. MAGIC-B (NCT00450203) is an on-going trial with the same chemotherapy noted previously in the initial MAGIC trial, but with the addition of adjuvant bevacizumab, and replaces infusional 5-FU with capecitabine. The recently reported Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial randomized patients with non-metastatic gastric adenocarcinoma treated with an upfront D2 resection to adjuvant chemotherapy (six cycles of capecitabine and cisplatin) or adjuvant chemoradiation (two cycles of capecitabine and cisplatin, then 45 Gy of radiation with capecitabine, and finally two additional cycles of capecitabine and cisplatin) [28]. A disease-free survival benefit was specifically seen in the subset of patients with node-positive disease, and this is now being independently investigated in the ARTIST II trial (NCT01761461). The question of perioperative chemotherapy versus adjuvant chemoradiation is being investigated on the on-going Dutch CRITICS trial [29].

Intensity-Modulated Radiation Therapy in Gastric Cancer

The location of the stomach within the left upper quadrant requires consideration of radiation dose to the lungs, heart, small and large intestines, liver, and kidneys. While prospective data on the use of IMRT in this patient population is limited, both retrospective and dosimetric data suggest potential benefits for normal tissue sparing.

As expected, most studies employing radiotherapy utilize this treatment modality in the adjuvant setting. Consequently, dosimetric comparison of target and normal tissues implies a postoperative bed into which normal tissues have likely migrated. Investigators at Stanford University reviewed their outcomes for gastric cancer patients treated in the adjuvant setting with either 3D-CRT or IMRT [30]. While disease-free survival (DFS) and OS were similar among the two groups, the use of IMRT resulted in a lower V20 dose to the kidney. Additionally, the serum creatinine remained unchanged in patients treated with IMRT, whereas a statistically significant increase was seen in patients treated with 3D-CRT (0.8–1.0, $p = 0.02$). A retrospective analysis of patients treated at The Netherlands Cancer Institute demonstrated a lower mean dose to the left kidney, resulting in a slower decline in glomerular filtration rate (GFR) as measured by technetium renography versus in patients treated with anterior-posterior/posterior-anterior (AP/PA) or 3D-CRT [31]. It should be noted, however, that while the rate of GFR decline was slower and the absolute GFR was higher in patients treated with IMRT, the overall GFR was lower in all groups.

VMAT has also been investigated in gastric cancer. A dosimetric comparison of 3D-CRT, IMRT, and VMAT radiation delivery methods was completed by researchers in China [32]. Mean dose to the target was improved using VMAT

versus IMRT. Additionally, the V20 of the liver was improved using VMAT versus IMRT. However, other dosimetric values were not statistically different between VMAT and IMRT. No clinical outcome data comparing VMAT and IMRT has been reported.

Charged Particle Therapy in Gastric Cancer

Proton therapy has also been investigated in the adjuvant treatment of gastric adenocarcinoma. A dosimetric analysis has been completed by investigators in Italy [33]. Proton therapy (2–3-field), 6-field photon IMRT, and 3D-CRT were compared. Dosimetrically, improvements were seen in mean radiation dose to the small bowel, liver, bilateral kidneys, and heart by using proton therapy. While thought-provoking and hypothesis-generating, no clinical outcomes can be inferred from this data.

Investigators from Japan have used definitive radiation therapy in patients with inoperable gastric cancers [34, 35]. Relatively high doses were used in these case reports (up to 86 Gy to the target volume), but results were intriguing, with patients found to be alive without recurrence 2 years posttreatment. However, aside from these early case reports, research on definitive proton beam or carbon therapy are lacking.

Pancreatic Cancer

The role of radiotherapy in pancreatic cancer is an evolving topic. Adjuvant radiation therapy has not been prospectively demonstrated to improve survival [36–39]; however, retrospective reports suggest that adjuvant chemoradiation (CRT) may have a local control and/or survival benefit in comparison with surgery alone [40–42]. The RTOG 0848 trial (NCT01013649) was opened in 2009 to determine the role of adjuvant fractionated CRT, by assessing whether gemcitabine plus erlotinib produces improved OS in comparison with gemcitabine alone and the role of RT (50.4 Gy) added to 5-FU- or capecitabine-based chemotherapy. The guidelines and an atlas for the delineation of the CTV used in this study were recently published [43].

While retrospective studies have demonstrated a benefit to using CRT over chemotherapy alone in locally advanced pancreatic cancer (LAPC) patients, conflicting results have been published [44–47]. The NCCN guidelines recommend an initial course of chemotherapy followed by CRT in order to maximize systemic and local control and to select patients who are most likely to benefit from CRT. The Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) LAP 07 trial was designed with the goal of defining the role of IMRT after chemotherapy in patients with locally advanced pancreatic cancer [48]. The data demonstrated no significant difference in OS between the two arms (15.2 vs. 16.5 months, $p = 0.83$) although, notably, the CRT group was associated with decreased local failure rates (32% vs. 46%, $p = 0.03$). It is important to note that only a small proportion of patients went to surgery, but their median survival was 30 months. This suggests that select patients with LAPC may benefit from surgery after maximal neoadjuvant therapy.

Most recently, RT has evolved to play a large role in neoadjuvant therapy in patients with borderline resectable and locally advanced disease. A meta-analysis of neoadjuvant therapy in pancreatic cancer reported on 4394 borderline resectable and locally advanced patients enrolled in 111 trials [49]. Although the authors did not stratify by radiation delivery, the Response Evaluation Criteria In Solid Tumors (RECIST) criteria showed a favorable disease control rate of 77%, including a 5% complete response rate, 30% partial response, and 42% stable disease. Nearly half (47%) of the initially unresectable patients underwent surgical exploration, with an overall resection rate of 33% and an R0 resection rate of 79%. Median OS among resected and unresected patients was 20.5 and 10.2 months, respectively.

Intensity-Modulated Radiation Therapy in Pancreatic Cancer

As technologies have advanced in recent decades, IMRT has surpassed 3D-CRT as the standard of care technique for conventional CRT in pancreatic cancer. Associated with favorable toxicity and potentially improved quality of life (QOL) in comparison with 3D-CRT [50, 51], IMRT is particularly appealing for patients with the tumor or tumor bed in close proximity with radiosensitive normal structures such as the duodenum, stomach, bowel, and esophagus. Furthermore, IMRT allows for dose escalation that may lead to improved local control, especially in patients with margin-positive resections treated adjuvantly [52].

Most recently, Prasad and colleagues from the Memorial Sloan Kettering published on GI toxicity in patients with LAPC receiving IMRT [53]. In comparison with 3D-CRT, IMRT was associated with significantly lower grade ≥ 2 GI toxicity. A recent Korean study also revealed that patients receiving 3D-CRT have significantly more gastroduodenal ulcers ($p = 0.003$) and are at increased risk for GI toxicity (OR, 11.67; $p = 0.01$) [54]. RTOG 1201 was a phase III trial currently open to compare dose-intensified chemoradiotherapy using IMRT (63.0 Gy) versus standard dose using 3D-CRT or IMRT (50.4 Gy). Patients were to be stratified by SMAD4 status, a potential biomarker that may correlate with patterns of disease progression, as intact SMAD4 was suggested to correlate with a locally destructive phenotype [55]. However, due to the results of the LAP 07 trial and low enrollment, the study was recently closed.

Volumetric Arc Therapy in Pancreatic Cancer

Numerous studies have compared the utility of IMRT versus VMAT in pancreatic cancer, and it appears that VMAT is associated with increased sparing of critical structures. One such study compared 3D-CRT, IMRT, and VMAT as neoadjuvant ($n = 4$) or adjuvant ($n = 8$) RT in borderline resectable pancreatic cancer (BRPC) or resectable pancreatic cancer [56]. Although the numbers are limited, this dosimetric comparison of normal tissue parameters revealed that VMAT was associated with the most critical structure sparing; although IMRT plans spared the liver and left kidney compared with 3D-CRT, VMAT plans spared these organs and significantly decreased dose to the small bowel (D10%, D15%), left kidney (V20), and stomach (V45) as well. Moreover, treatment planning and delivery times were most efficient for VMAT. These results are consistent with findings at Emory University, which reported similar or better sparing of abdominal organs with VMAT compared with IMRT [57]. Although VMAT has demonstrated dosimetric advantages over alternative RT approaches, it remains unclear whether this translates to decreased treatment-related toxicity or improved patient outcomes.

Stereotactic Body Radiation Therapy in Pancreatic Cancer

Pancreas SBRT has historically been evaluated most frequently in locally advanced disease, although its utility in borderline resectable, resected, and recurrent disease is emerging (Fig. 24.3). The combination of maximal chemotherapy with effective short-course RT makes SBRT an attractive option in pancreatic patients who are likely to progress distantly in a short period of time [58–60].

Early data published in Denmark demonstrated poor outcomes and unacceptable toxicity associated with 45 Gy SBRT in three fractions (15 Gy per fraction) and subsequently caused investigators to question the role of pancreas SBRT [61]. Stanford University has contributed seminal data that single-fraction SBRT (25 Gy × 1) results in local control but with questionable GI toxicity [62–64]. Therefore, a prospective multicenter phase II trial among Stanford University, Johns Hopkins University, and MSKCC was designed to evaluate if fractionated SBRT (33 Gy SBRT in five fractions) would result in similar local control (94% at 1 year) with improved GI toxicity [65]. Median OS was 13.9 months, local control was comparable at 78%, QOL scores were stable, and rates of grade ≥ 2 acute (2%) and late (11%) toxicity were minimal. Overall, delivery of fractionated (3–5 fractions) SBRT demonstrates favorable tumor response rates (~30%) and less acute toxicity compared with conventional CRT in patients with LAPC [66–68]. Nonetheless, additional studies are necessary to evaluate the optimal dose and timing of fractionated SBRT.

More recently, SBRT has been evaluated in the neoadjuvant setting in patients with borderline resectable and locally advanced pancreatic cancer. The largest report of pancreas SBRT in patients with borderline resectable disease was recently published by colleagues at Moffitt Cancer Center [69]. The 159 patients (110 borderline resectable [BR], 49 locally advanced [LA]) included in the study received induction chemotherapy (most commonly gemcitabine, docetaxel, and capecitabine [GTX] in 81%) followed by 30 Gy SBRT in five fractions. The overall rate of resection was 38%, with 51% in BRPC and 10% in LAPC successfully undergoing surgery. The overall margin-negative resection rate was 97%, with 96% of BRPC and 100% of LAPC patients achieving negative margins. Johns Hopkins University also reported on 88 with BRPC ($n = 14$) and LAPC ($n = 74$) who were treated with definitive 5-fraction SBRT treated to a total dose of 33 Gy [70]. Thirty-two (80%) of the 74 patients with LAPC were treated on the previously mentioned multi-institutional clinical trial [65]. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Prior to SBRT, the majority (88%) of patients were treated with gemcitabine-based or FOLFIRINOX (folinic acid [leucovorin], 5-fluorouracil, irinotecan, oxaliplatin) multi-agent chemotherapy. In this report, 29% of BRPC and 20% of LAPC patients successfully underwent surgery. Of these, the margin-negative resection rate was 84% overall, with a margin-negative resection rate of 84% and 80% in BRPC and LAPC, respectively. In both of these manuscripts, distant progression remained the primary reason for which patients did not undergo surgery, therefore conveying the need for more effective systemic therapies.

Less frequently, pancreas SBRT is used in the case of salvage re-irradiation after prior CRT. Three publications have published on SBRT re-irradiation after an initial median dose of 50.4 Gy CRT. Lominska and colleagues at the University of Kansas reported on a median of 23 Gy SBRT delivered to 28 previously irradiated patients [71]. Median OS was 5.9 months from SBRT and local control was 86%. Two cases of late grade 3 GI toxicity (7%) were reported. Wild and colleagues at Johns Hopkins and Stanford reported a multi-institutional experience of 18 patients who received re-irradiation [72]. Median OS after SBRT was 8.8 months and local control was 62%. Only one patient (6%) experienced a grade 3 GI toxicity. Dagoglu and colleagues at Beth Israel just published on their experience of 30 patients treated with 25 Gy SBRT re-irradiation [73]. Local control was 78% in this cohort and median OS was impressive at 14.0 months. Two patients experienced late grade 3 toxicity consistent with bowel obstruction.

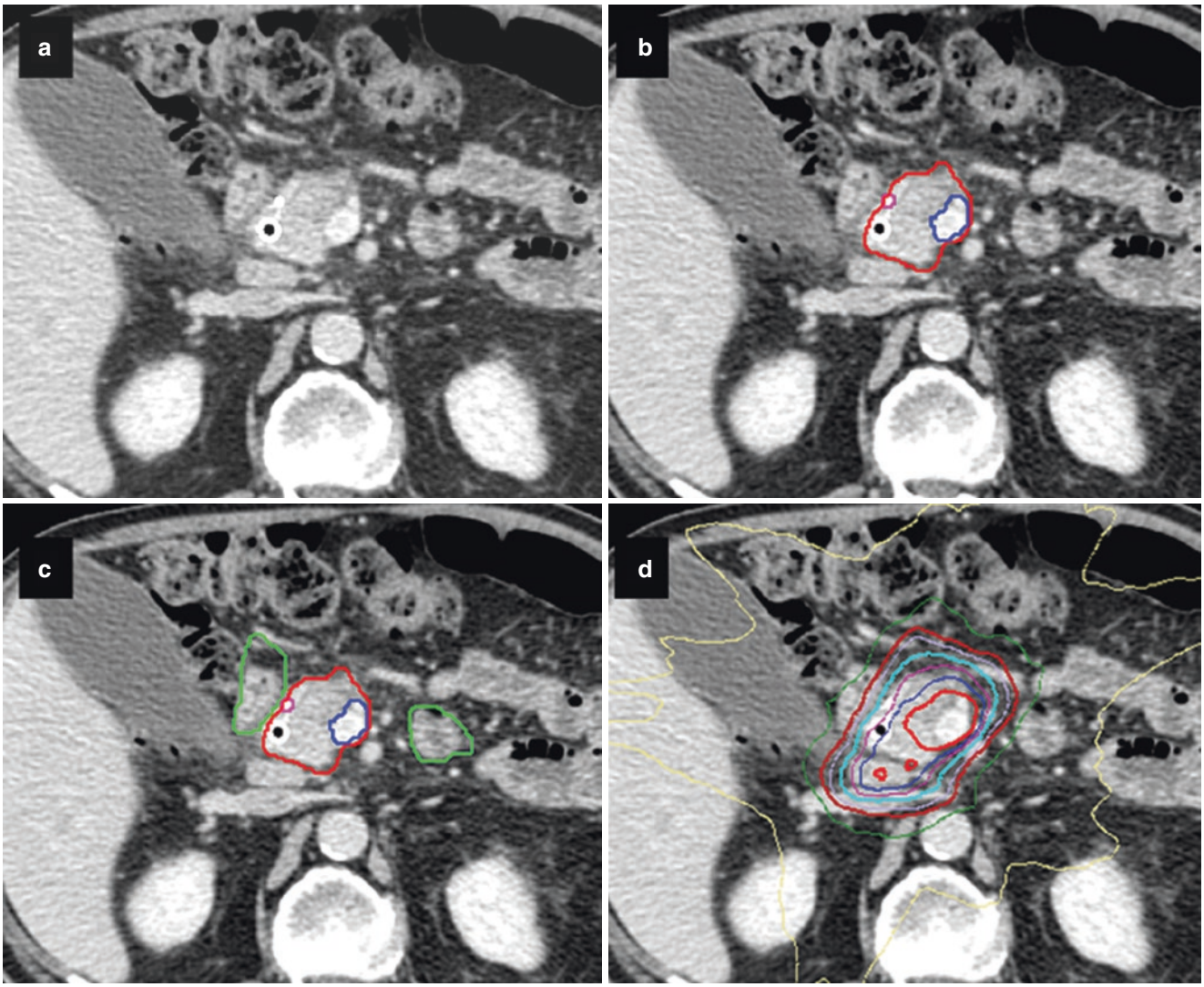


Fig. 24.3 Representative example of pancreas SBRT planning and treatment delivery. (**a**) Radiation planning CT scan (simulation) with IV contrast identifies a mass at the head of the pancreas. (**b**) The pancreas mass is drawn (red) and is seen to abut the portal vein (blue), and a fiducial is placed prior to the simulation (pink). (**c**) The nearby duodenum is drawn as an avoidance structure. (**d**) Radiation planning is completed with dose maximally delivered around the tumor abutting the portal vein (red – 40 Gy in five fractions), prescription dose delivered to the entire pancreas mass (light blue – 33 Gy in five fractions), and rapid fall-off in dose to avoid the adjacent duodenum (maroon – 25 Gy in five fractions)

Particle Therapy in Pancreatic Cancer

Massachusetts General Hospital (MGH) reported results of a phase I/II trial of neoadjuvant proton therapy to 25 Gy in five fractions with concurrent capecitabine followed by surgical resection and adjuvant gemcitabine delivered to patients with resectable pancreatic cancer [74]. Of the 35 patients, only 4% were observed to have grade ≥ 3 GI toxicity. Interestingly, 22% of patients did not undergo surgery due to change in diagnosis (2%), metastatic progression (4%), or unresectable disease at the time of exploration (16%). The node-negative resection rate was reported to be very low at 19%, whereas 84% had a margin-negative resection. Median OS was 17.3 months, with 42% of patients surviving 2 years, and median progression-free survival (PFS) was 10.4 months. Of the 37 resected patients, median OS and PFS were 27.0 months and 14.5 months, respectively. At median follow-up of 38 months, 16% of the resected patients had recurred locoregionally. Proton therapy has also been reported in patients with LAPC and found to be extremely tolerable (0–10% grade ≥ 3 toxicity) [75, 76]. Interestingly, however, a follow-up report of the Japanese study performed endoscopy post-SBRT, and it was observed that 49% of patients had radiation-induced gastric and duodenal ulcers (grade 1), though the rate of grade ≥ 3 toxicity was only 3% [77].

The University of Pennsylvania conducted studies comparing dosimetric data among proton and photon therapy in patients with pancreatic cancer. One study compared 3D-CRT with IMRT, VMAT, and passive scattering and modulated scanning proton therapy (PT) in patients receiving adjuvant RT to 50.4 Gy [78]. The study reported that all proton plans offered significantly lower doses to the left kidney (mean and V18Gy), stomach (mean and V20Gy), and spinal cord (maximum dose) compared with all the photon plans, except in the case of 3-field 3D-CRT with spinal cord maximum dose. Modulated scanning PT resulted in lower doses to the right kidney (mean and V18Gy), liver (mean dose), total bowel (V20Gy and mean dose), and small bowel (V15Gy absolute volume ratio) compared with all the photon plans and passive scattering PT. The dosimetric advantage of PT may allow for more tolerable dose-escalated RT to the tumor bed and comprehensive nodal areas. Another study evaluated 55 Gy delivered to patients with LAPC via double scattering (DS) and pencil beam scanning (PBS) proton therapy versus IMRT [79]. DS and PBS proton therapy were shown to decrease stomach, duodenum, and small bowel dose in low-dose regions compared to IMRT ($p < 0.01$). However, protons yielded increased doses in the mid-to-high dose regions and increased generalized equivalent uniform dose to the duodenum and stomach, although these differences were minimal (<5% and 10%, respectively; $p < 0.01$). This study suggests that proton therapy results in decreased low-to-intermediate dose to the treatment volume, although high dose of RT to organs at risk (OARs) was not significantly reduced. Additional study of the safety and efficacy of proton therapy in pancreatic cancer is warranted.

Image-Guided Therapy and Motion Management in Pancreatic Cancer

With IMRT and SBRT, the smaller field sizes can be detrimental if respiratory tumor motion is not accounted for. Pancreatic tumors can have respiratory motion at times greater than 2 cm craniocaudally [80]. If patients have ≥3 mm breathing motion on fluoroscopy or 4D CT scan, tumor immobilization techniques should be utilized [58]. Two approaches to motion management are commonly employed: immobilization of the target (abdominal compression or breath-hold techniques) and physiologically monitoring of tumor motion (tracking or gating) [60]. Generally, if breathing motion is <3 mm, patients can be treated free-breathing with an internal target volume (ITV) based on the 0% and 50% phases of the breathing cycle or using gating. In these patients, a PET or MRI simulation may improve the ability to delineate the tumor and adjacent structures as well as provide a baseline to determine treatment response.

Positron Emission Tomography and Radiation Therapy in Pancreatic Cancer

Although the literature is sparse, two prospective studies have published on the role of PET in patients with LAPC who received SBRT. In patients treated with gemcitabine and single-fraction 25 Gy SBRT ($n = 55$), both maximum standardized uptake value (SUVmax) and metabolic tumor burden (MTB) were associated with a 5- and 8-month OS benefit, respectively [81]. Clinical SUVmax persisted as an independent predictor for OS ($p = 0.03$) and progression-free survival ($p = 0.03$) on multivariate analysis. More recently, a phase II multi-institutional study evaluating gemcitabine and 33 Gy SBRT in LAPC, PET avidity at baseline was the strongest predictor of an increased risk of death on multivariate analysis (hazard ratio, 2.87; 95% confidence interval [CI], 1.26–6.50, $p = 0.012$) [65]. Furthermore, the median maximum standardized uptake value (SUVmax) was shown to decrease from pre- to post-SBRT (from 4.75 g/mL to 3.15 g/mL; $p = 0.001$).

Hepatocellular Carcinoma

Given that hepatocellular carcinoma (HCC) typically arises in the context of liver cirrhosis, underlying injury to the liver is common and an important factor in determining treatment recommendations. The majority of patients will succumb to disease progression within the liver; therefore, an important goal in seeking therapy involves local tumor control while preserving liver function. Of note, the toxicity observed with radiotherapy for HCC is greater than that seen with liver metastases, generally due to pre-existent liver dysfunction.

Stereotactic Body Radiation Therapy in Hepatocellular Carcinoma

SBRT offers a less invasive technique to maximize local control while minimizing RT exposure to normal liver tissue in patients with hepatic dysfunction. SBRT is primarily recommended for patients with early stage tumors up to a maximum size of 6 cm and ideally located >1 cm from luminal GI organs at risk [82].

Two sequential phase I and II studies of SBRT in 102 HCC patients with median tumor size of 7 cm reported by colleagues at Princess Margaret Cancer Center (PMCC) established the foundation of SBRT in HCC [83]. The locoregional control rate at 1 year was favorable at 87%; however, the rate of grade ≥ 3 toxicity was high at 30% and appears that 7% of patients may have died due to causes related to treatment. The same group also reported quality of life outcomes, demonstrating no decrease in QOL although liver

SBRT resulted in a temporary detriment in appetite and fatigue [84].

Recently published was a single-arm phase I trial conducted at PMCC aiming to evaluate maximally tolerated doses of sorafenib administered before, during, and after six fractions of SBRT, with stratification by low (<30%) versus high (30–60%) effective irradiated liver volume (<30%) [85]. Although survival has not yet been reached, preliminary data reveal that significant toxicity resulted and this combination is not recommended outside the setting of a clinical trial. The RTOG 1112 is aiming to compare sorafenib alone versus SBRT alone followed by daily sorafenib in patients with vascular involvement.

Some large, unresectable tumors may be difficult to efficiently treat with SBRT [86]. In these patients, simultaneous integrated boost (SIB) consisting of a combination of hypofractionation and dose painting with motion management and image guidance techniques may be a safe and effective alternative and is shown in Fig. 24.4 [87]. This SIB technique may be employed with proton or photon therapy to deliver very high doses (up to 140 Gy BED). An attractive option, it appears to be feasible yet rates of local control are unknown.

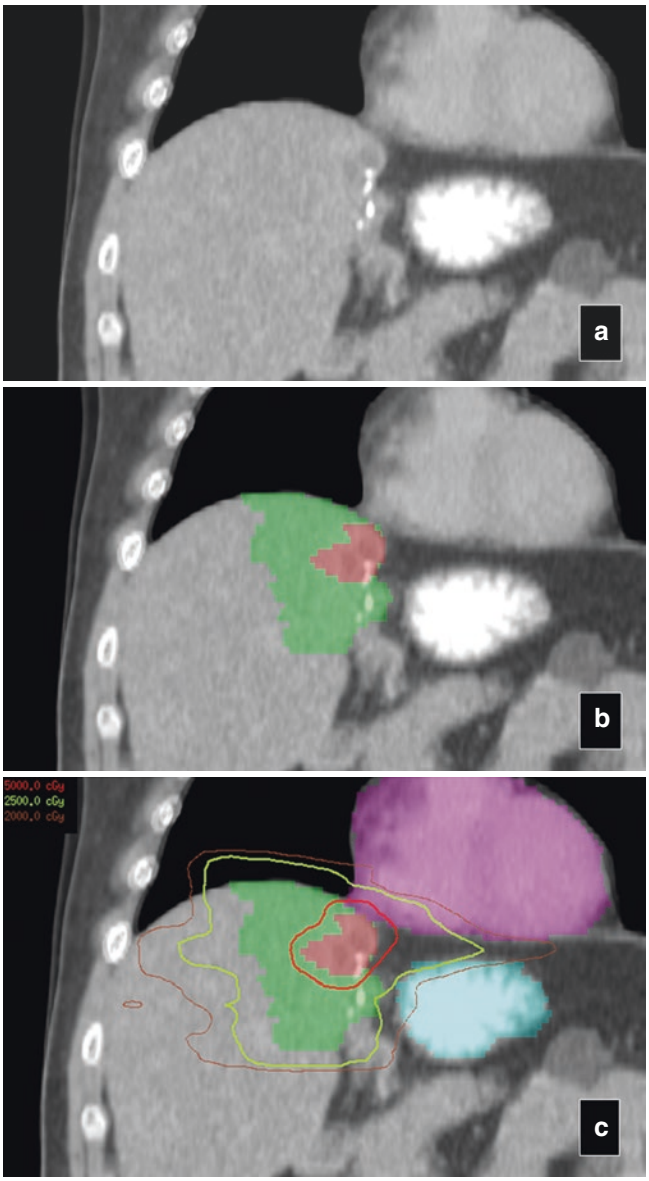


Fig. 24.4 An SBRT plan for liver metastases using simultaneous integrated boost (SIB) is shown. (**a**) A coronal slice is presented showing a hypodense lesion along the left (medial) edge of the liver with adjacent clips. The stomach is visible with oral contrast. (**b**) The red shaded area represents the metastatic deposit, and the green shaded area demonstrates the resection bed and segment 8 of the liver. (**c**) Radiation dose is given to the metastatic tumor volume to a dose of 50 Gy in five fractions (red isodose line). A lower dose of 25 Gy in five fractions (yellow isodose line) is given to the resection bed and remainder of segment 8. Note that the yellow line curves away from the stomach (light blue shading), demonstrating the ability of this technique to reduce gastrointestinal toxicity

Particle Therapy in Hepatocellular Carcinoma

Particle therapy appears to have advantages in HCC due to its ability to sharply penetrate tissue and deposit maximum energy. Proton therapy and carbon-ion radiation for HCC have historically been reported to be effective and well tolerated for advanced tumors.

A recent Japanese study compared particle therapy with carbon ions (passive scattering) versus photon therapy with SBRT in patients with HCC [88]. Ten patients received 60 Gy carbon-ion RT in four fractions, after which a treatment plan of 60 Gy in four fractions of SBRT was simulated and created by a single radiation oncologist. The PTV D90 was 59.6 ± 0.2 Gy for carbon-ion RT in comparison with 56.6 ± 0.3 Gy for SBRT ($p < 0.05$). Homogeneity index and conformity index were 1.19 ± 0.03 and 0.79 ± 0.06, respectively, in carbon-ion RT, as compared to 1.21 ± 0.01 and 0.37 ± 0.02, respectively, in SBRT, with only CI resulting in a significant difference between two modalities. Mean liver dose was 8.1 ± 1.4 Gy in carbon-ion RT, as compared to 16.1 ± 2.5 Gy in SBRT ($p < 0.05$). V5 to V50 were higher in SBRT than carbon-ion RT, and significant differences were observed for V5, V10, and V20. Therefore, this small dataset suggests that carbon-ion RT may be superior in target conformity and sparing of normal liver tissue in comparison with SBRT.

On a larger scale, Qi and colleagues in China conducted a meta-analysis on photon ($n = 3577$) versus proton ($n = 1627$) therapy in HCC [89]. Pooled OS was significantly higher at 1, 3, and 5 years for proton therapy as opposed to photon therapy (relative risk [RR] 1.68, 95% CI 1.22–2.31; $p < 0.001$; RR 3.46, 95% CI 1.72–3.51, $p < 0.001$; RR 25.9, 95% CI 1.64–408.5, $p = 0.02$, respectively). Progression-free survival and local control at longest follow-up were also significantly higher with proton therapy than for photon therapy ($p = 0.013$ and $p < 0.001$, respectively), while comparable efficacy was

observed when comparing proton therapy and SBRT in terms of OS, PFS, and LC at longest follow-up. High-grade acute and late toxicity was also reported to be lower with proton therapy. While these outcomes are promising, concerns of the generalizability among numerous other limitations of the analysis were subsequently reported [90–92].

Oligometastatic Disease to the Liver

SBRT has been evaluated in patients with oligometastases to the liver. In one retrospective study, Lanciano and colleagues at Drexel University reported on 30 patients treated with ablative SBRT ($BED_{10} \geq 79.2$Gy) after being heavily treated with systemic (87%) and/or liver-directed therapy (37%) [93]. Of the 30 patients, 23 (77%) were being treated for liver metastases, while the remaining had cholangiocarcinoma (13%) or HCC (10%). At a median follow-up of 22 months, 36% of patients experienced local failure. A decrease in local failure was found with higher doses of SBRT ($p = 0.0237$); 55% of tumors receiving a $BED_{10} \leq 100$ Gy had local failure compared with 19% receiving a $BED_{10} > 100$ Gy. The 2-year actuarial rate of local control for tumors treated with $BED_{10} > 100$ Gy was 75% compared to 38% for those patients treated with $BED_{10} \leq 100$ Gy ($p = 0.04$). Overall, seven patients (23%) remain alive with a median OS time of 20 months from SBRT and 57 months from diagnosis. In conclusion, it appears that SBRT was well tolerated despite the large amount of prior therapy and resulted in favorable rates of local control.

Stanford University also published on toxicity involving SBRT in primary (53%) and metastatic (47%) liver lesions [94]. Median BED_{10} was 85.5 Gy (range 37.5–151.2) for a median of five fractions (range, 1–5). Rates of GI toxicity included 24% grade ≥ 2 and 19% grade ≥ 3. Clinical factors associated with grade ≥ 3 GI toxicity were cholangiocarcinoma histology ($p < 0.0001$), primary liver tumor ($p = 0.009$), and a biliary stent ($p < 0.0001$). Dosimetric parameters most predictive of grade ≥ 3 toxicity were volume receiving above BED_{10} of (1) 72 Gy ≥ 21 cm^3 (relative risk 11.6, $p < 0.0001$) and (2) 66 Gy ≥ 24 cm^3 (RR 10.5, $p < 0.0001$) as well as mean BED_{10} to the central hepatobiliary tract ≥14 Gy (RR 9.2, $p < 0.0001$). This study may be utilized to determine dose constraints to improve future treatment-related toxicity in liver SBRT. An example of SBRT to liver metastases with an SIB technique is shown in Fig. 24.4.

Cholangiocarcinoma

Making major strides in therapeutic delivery for cholangiocarcinoma is particularly problematic due to its rarity and difficult anatomic location that subsequently result in grouping of cholangiocarcinoma with other hepatobiliary malignancies such as hepatocellular carcinoma or gallbladder cancer. Often delivered in the adjuvant, unresectable, or recurrent setting, radiation therapy offers an improvement in quality and quantity of life by maximizing local control.

A recent study reported on unresectable intrahepatic cholangiocarcinoma patients receiving ablative radiation with BED ≤ 80.5 Gy ($n = 60$) versus >80.5 Gy ($n = 19$) from 2002 to 2014 [95]. Approximately half of patients received IMRT, while the remaining received 3D proton (32%) or photon (16%) therapy. The median tumor size at diagnosis was 7.9 cm (range, 2.2–17). Median follow-up time was 33 months. Median OS was 30 months and the rate of 3-year OS was 44%. The 3-year OS (73% vs. 38%, $p = 0.017$) and local control (78% vs. 45%, $p = 0.04$) rates for patients receiving BED > 80.5 Gy were significantly higher in comparison with BED ≤ 80.5 Gy. The investigators concluded that high-dose RT is predictive of improved local control and OS and a BED > 80.5 Gy appears to be an ablative dose in patients with large IHCC tumors.

Evidence of a dose-response relationship in cholangiocarcinoma has been reported, yet a majority of patients will fail within the radiation field despite the use of doses >45 Gy [82]. This has prompted investigation into the use of SBRT as a method for dose escalation. In general, higher local control rates have been seen with SBRT in comparison with 3D-CRT trials, and this may be a promising way forward. One advantage of SBRT is the short overall treatment time, allowing easier integration with multimodality therapies.

An alternative to dose escalation may be the use of a brachytherapy boost. Italian colleagues recently reported on their experience with gemcitabine chemoradiation in 27 patients with unresectable extrahepatic cholangiocarcinoma. [96] A total dose of 50.4 Gy was delivered to the tumor and 39.6 Gy to lymph nodes using 3D-CRT followed by a boost with a median dose of 15 Gy (range, 15–20) intraluminal high-dose-rate brachytherapy with 192 Ir in select patients (22%). Median follow-up was 16 months, with a 2-year local control rate of 29%. Two-year and 3-year OS rates were 27% and 7%, and median OS was 14 months. The brachytherapy boost demonstrated a 7-month advantage (21 vs. 14 months, no p-value reported). Acute grades 3 and 4 GI toxicities were observed in 15% and 4% of patients, respectively, whereas no late toxicity was experienced. It appears that the brachytherapy boost improved long-term outcomes; however, additional investigation is necessary to validate this on a larger scale.

Stereotactic Body Radiation Therapy in Cholangiocarcinoma

SBRT in cholangiocarcinoma is most commonly delivered in unresectable cases, with 1-year OS rates after SBRT range

from 45% to 73% [97–99]. A study on hilar lesions revealed impressive rates of progression-free survival (30 months), 2-year OS (80%), and 4- year OS (30%) although the numbers were small ($n = 10$) [100].

Particle Therapy in Cholangiocarcinoma

Though particle therapy has been thoroughly studied in hepatocellular carcinoma, the role of proton therapy in cholangiocarcinoma is less understood. One report involved 28 unresectable or recurrent cholangiocarcinoma patients (including 21% intrahepatic, 21% hilar, 11% extrahepatic, 11% gallbladder, and 36% local or nodal recurrence) receiving a median BED of 68.2 Gy [101]. Median follow-up was 12 months, with 1-year OS of 49% and 1-year local control of 68%. Age ≥ 70 (10 vs. 14 months, $p = 0.03$) and ECOG > 1 (5 vs. --, $p < 0.0001$) were significant factors for inferior OS, while a $BED_{10} > 70$ Gy was predictive of improved local control at 1 year (83% vs. 22%, $p = 0.002$). Rates of grade 3, 4, and 5 toxicity were 29%, 0%, and 0% for overall reasonable toxicity. An additional study reported on 20 patients with unresectable intrahepatic cholangiocarcinoma received proton therapy in Japan [102]. The median maximum tumor size was 5 cm (range, 1.5–14), with a median total dose of 72.6 Gy delivered to the intrahepatic region within 22 fractions and 56.1 Gy delivered to the lymph nodes in 17 fractions. Of note, eight patients were reported to have been treated palliatively due to tumor presence outside the radiation field. Median OS in the curative group was 27.5 months, with rates of 1- and 3-year OS at 82% and 38%, respectively. At median time of follow-up of 20.8 months, the rate of local control was 75% in the curative group. No grade ≥ 3 toxicity was reported. Therefore, it appears that proton therapy may be a feasible option for providing local control in advanced patients.

A phase II multi-institutional study recently reported by Hong and colleagues evaluated the role of high-dose, hypofractionated proton beam therapy for HCC ($n = 44$) and intrahepatic cholangiocarcinoma ($n = 37$) [103]. The median maximum tumor dimension in cholangiocarcinoma patients was 6.0 cm (range, 2.2–10.9), 62% of patients received therapy prior to radiation, and the median dose of radiation delivered was 58.0 Gy. Median follow-up time was 19.5 months, with a 94% rate of local control at 2 years. OS at 2 years was 47%. The rate of grade 3 radiation-related toxicity was 8%, while no grade 4 or 5 toxicity was observed.

Gallbladder Cancer

The role of adjuvant radiation therapy in gallbladder cancer is largely unknown, and conflicting studies have been published. A recent analysis of the National Cancer Database on 6690 patients with resected gallbladder cancer reported that adjuvant chemoradiation was associated with improved OS for all patients (HR 0.77, 95% CI 0.66–0.90), especially those who underwent a node-positive resection (HR 0.64, 95% CI 0.53–0.78) [104]. Among patients with unknown lymph node status, those with T2 or T3 disease saw improved OS with adjuvant chemoradiation (T2, HR 0.79, 95% CI 0.63–0.99; T3, HR 0.43, 95% CI 0.30–0.62). Median OS was 18.0 months, 12.4 months, and 21.2 months among patients who received no adjuvant therapy, adjuvant chemotherapy alone, and adjuvant chemoradiation, respectively.

A multi-institutional retrospective report at Johns Hopkins University, Mayo Clinic, Duke University, Oregon Health & Science University, the University of Michigan, and the University of Texas MDACC between 1985 and 2008 demonstrated a median OS of 60.5 months and 5-year OS rate of 51% [105]. On multivariate analysis, lymph node involvement was a significant factor for inferior OS (HR 4.81, 95% CI 2.20–10.52, $p < 0.01$), while surgery after the year 2000 was associated with superior OS (HR 0.21, 95% CI 0.10–0.45, $p < 0.01$). The Southwest Oncology Group was the first to prospectively evaluate the role of adjuvant chemoradiation in extrahepatic cholangiocarcinoma and gallbladder cancer with the S0809 trial [106]. A total of 79 patients (32% gallbladder cancer) were adjuvantly treated with 4 cycles of gemcitabine and capecitabine followed by concurrent capecitabine and 52.5–54 Gy radiation. The rate of 2-year OS was impressive at 65%, with a median OS time of 35 months. Grade 3 and 4 toxicity rates were 52% and 11%, respectively, and most consistent with neutropenia, hand-foot syndrome, diarrhea, lymphopenia, and leukopenia. One GI bleed (1%) possibly attributed to radiation resulted in death. Overall, it appears that this regimen is safe and effective, providing the foundation for phase III trials in the future. While adjuvant radiation appears to be associated with long-term benefits, the data is in its infancy, and advanced radiation techniques have not undergone study. It is suggested that adjuvant SBRT may be a safe and effective option for resected gallbladder patients, although larger study numbers are necessary [107].

Rectal Cancer

Appropriate oncologic resection with a total mesorectal excision remains the recommended therapy for patients with operable rectal adenocarcinoma [108, 109]. However, there is clear consensus in the GI oncology community that a local control benefit exists from the use of neoadjuvant or adjuvant chemoradiation [110]. A meta-analysis completed by the Colorectal Cancer Collaborative Group in 2001 compared the results of rectal cancer trials comparing neoadjuvant radiation therapy to surgery alone and adjuvant radiation

therapy to surgery alone [111]. While no OS benefit was seen in this meta-analysis (62% without radiotherapy versus 63% with radiotherapy, $p = 0.06$), both neoadjuvant and adjuvant radiation therapy schedules resulted in improved local control (46% yearly risk reduction with neoadjuvant radiation [$p = 0.00001$] and 37% yearly risk reduction with adjuvant radiation [$p = 0.002$]). Consequently, surgery alone is not recommended for most patients with operable rectal adenocarcinoma.

Findings from the German Rectal Cancer Study Group trial investigating neoadjuvant versus adjuvant chemoradiation in T3/T4 or node-positive rectal cancer are the backbone of treatment for most patients with resectable disease [112]. This study demonstrated that 3D-CRT to a dose of 50.4 Gy with infusional 5-FU prior to surgery resulted in lower 5-year local relapse rates than patients treated in the adjuvant setting with 55.8 Gy of 3D-CRT and the same chemotherapy (6 versus 13%, $p = 0.006$). Five-year OS and disease-free survival were similar between the groups. Both acute (27 versus 40%, $p = 0.001$) and late (14 versus 24%, $p = 0.01$) grade 3–4 toxicities were lower in patients treated in the neoadjuvant setting. The 10-year update of this data has also been recently reported [113]. The previously noted local relapse rate remained statistically lower in patients treated with neoadjuvant chemoradiation (7.1 versus 10.1%, $p = 0.048$). Again, no differences were seen in OS, disease-free survival, or incidence of distant metastatic disease.

In addition to the reduced rate of local failure previously noted, neoadjuvant therapy has become the standard of care in patients with T3/T4 or node-positive rectal cancers to allow for tumor downstaging (potentially identifying patients with more favorable tumor biologies) and sphincter preservation at the time of surgery, a reduced radiation dose in the neoadjuvant setting, and smaller radiation fields (not having to radiate a surgically violated field). However, in an attempt to help reduce toxicity associated with radiation, researchers have investigated both IMRT and proton beam therapy to help avoid normal toxicity.

Intensity-Modulated Radiation Therapy in Rectal Cancer

As with most disease sites, retrospective dosimetric analyses have shown improved target coverage and normal tissue sparing with IMRT compared to 3D-CRT [114–116]. Clinical data comparing IMRT to 3D-CRT was published by Samuelian and colleagues in 2012 [117]. They retrospectively compared 61 patients treated with 3D-CRT to 31 patients treated with IMRT. Doses between the two groups were similar, though the IMRT plans used a simultaneous integrated boost technique. The investigators found that IMRT reduced the incidence of grade 2 or greater GI toxicity versus the use of 3D-CRT (48 versus 62%, $p = 0.006$). Specifically, IMRT reduced the rate of diarrhea and enteritis when compared to 3D-CRT. No significant differences in non-GI toxicities were observed. Although GI toxicity was reduced, IMRT did not result in fewer treatment breaks or a reduction in early termination of therapy.

The RTOG has prospectively investigated the role of IMRT in its phase II clinical trial 0822. This prospective single-arm study treated patients with cT3-4Nx or cTxN1-2 rectal adenocarcinoma patients with neoadjuvant IMRT + capecitabine + oxaliplatin followed by surgery and adjuvant chemotherapy. The primary endpoint was grade 2 or greater GI toxicity (28%) in comparison to the oxaliplatin arm of RTOG 0247 in which 3D-CRT was used [118]. The rate of grade ≥ 2 GI toxicity was 51.5% with IMRT and 40% with 3D-CRT, clearly not meeting the pre-defined endpoint of RTOG 0822 [119]. Central plan review demonstrated that the vast majority (93%) of submitted radiation volumes were accurate and followed protocol. One criticism of this trial's outcome is the possibility that the higher rate of side effects may be due to the use of oxaliplatin.

Despite the results of the aforementioned prospective trial, IMRT remains an area of active investigation in rectal cancer, and it is likely that future trials will allow IMRT as a reasonable delivery option for radiation therapy. For contouring recommendations in IMRT, the RTOG has an atlas of target structures and reasonable volumetric expansions (www.rtog.org/CoreLab/ContouringAtlases/Anorectal.aspx).

Charged Particle Therapy in Rectal Cancer

As early as 1992, data had emerged from MGH regarding a potential benefit for proton therapy in rectal cancer. A dosimetric analysis by Tatsuzaki indicated that proton beam therapy was able to reduce the volume of small bowel irradiated in comparison to three different 3D-CRT plans (AP/PA and 3-field and 4-field box) [120]. Similarly, a Swedish analysis in 1996 showed a small benefit of proton beam therapy to reduce dose to the small bowel, bladder, and femoral heads versus 3D-CRT [121].

More recently, investigators from the Florida Proton Institute completed a dosimetric analysis of proton beam therapy to both 3D-CRT and IMRT in patients with resectable rectal cancer [122]. Compared to 3D-CRT and IMRT techniques, proton beam therapy was able to reduce bone marrow V5Gy, V10Gy, V15Gy, and V20Gy ($p = 0.0156$ for each). Similarly, proton beam therapy reduced small bowel V10Gy, V20Gy, and V30Gy doses compared to 3D-CRT ($p = 0.0156$ for each) but only reduced V10Gy and V20Gy small bowel doses compared to IMRT ($p = 0.0156$ for each). In terms of bladder sparing, proton beam therapy reduced

bladder V40Gy compared to 3D-CRT (p = 0.016), but no improvement was seen compared to IMRT. The authors note the potential benefit proton beam offers, particularly in terms of the bone marrow toxicity reduction that may impact future chemotherapy options.

As of the writing of this text, published clinical data on the outcomes of proton beam therapy in rectal cancer are wanting. However, the use of carbon-ion therapy in recurrent rectal cancer has been reported. A series of three case reports were published by Japanese investigators on patient outcomes following local recurrence of rectal cancer and subsequent treatment with carbon-ion therapy [123]. All patients were treated to at least 70.4 GyE in a minimum of 2 GyE per fractions. All patients were local recurrence-free at least 2 years following therapy though a thorough reporting of radiation details and toxicity was not completed.

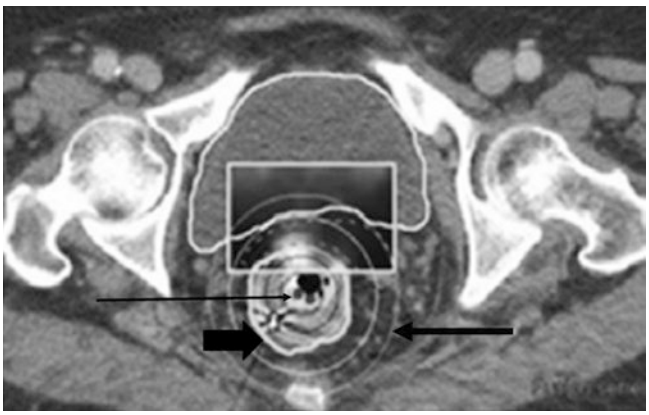


Fig. 24.5 A representative section of dose distribution with endorectal brachytherapy (EBT) is shown with demonstration of rapid dose fall-off. The long, narrow arrow demonstrates the center of the lumen with the brachytherapy catheter. The short, thick arrow demonstrates the high-dose region (the 100% isodose line). The medium thickness, medium length arrow demonstrates the low-dose region (the 30% isodose line). (Reprinted with permission from Smith et al. [126])

Endorectal Brachytherapy

Brachytherapy is a technique of providing radiation in direct approximation to a tissue surface. In contrast to external beam radiation, it often provides high doses of radiation near a target site with minimal radiation dose to surrounding structures due to rapid dose reduction over a given distance. Rectal cancer provides a unique opportunity to use this type of therapy due to the presence of the tumor in an accessible hollow cavity, thereby allowing brachytherapy by placing a radioactive source material directly in contact with the target lesion.

Vuong and colleagues first reported their results of this technique in a phase I/II trial published in 2002 [124]. Patients with operable T2 to early T4, N0–N2 lesions were treated using four fractions of 6.5 Gy of daily radiation (total dose of 26 Gy) to the tumor and radial margin, followed by surgery 4–8 weeks later. If positive nodes were identified in the final pathology specimen, adjuvant external beam radiation was applied to a dose 45 Gy in 25 fractions with concurrent chemotherapy. The results of the study demonstrated an astounding complete clinical response rate of 68% on endoscopic rectal ultrasound following therapy, with a 32% pathologic T0 N0–N1 rate, and an additional 36% with only residual microfoci of carcinoma. These results were updated in a 2007 publication [125]. Again, the pathologic complete response rate (T0) was 29% with 37% showing microfoci of residual disease. The 5-year local recurrence rate was 5%, disease-free survival was 65%, and OS was 70%. Local toxicity was significant, however, with 99% of patients suffering grade 2 proctitis and 1% of patients suffering grade 3 proctitis in 7–10 days immediately following treatment. Surgical complication rates were low.

Investigators from the Johns Hopkins University compared their early results of patients treated with endorectal brachytherapy to patients treated with neoadjuvant external beam radiation (IMRT or 3D-CRT) during the same time period [126]. A representative section of dose distribution with EBT is shown in Fig. 24.5. This report is limited by its small sample size (n = 7 for endorectal brachytherapy, n = 25 for external beam radiation) but demonstrates a trend toward improved pathologic complete response rate for endorectal brachytherapy (43% versus 12%, p = 0.06). Progression-free survival and OS were similar between the endorectal brachytherapy group and external beam patients. Data has also been reported on the use of endorectal brachytherapy in the re-irradiation setting, though this remains hypothesis-generating at this time [127].

A 2015 American Society for Radiation Oncology (ASTRO) Clinical Practice Statement was published in 2015 to outline the appropriate customization of radiation therapy in stage II and III rectal cancers [128]. Neoadjuvant endorectal brachytherapy alone was felt to be "rarely appropriate" by the panel, owing largely to the paucity of data, particularly randomized data, on this modality. As its use expands and its optimal role in therapy is elucidated, prospective data will help to define its true role in the treatment of de novo and recurrent rectal cancer.

Anal Cancer

Unlike most other malignancies in the GI tract, most anal carcinomas originate from squamous epithelium. As this histology is generally more radiosensitive than adenocarcinomas, most sites of primary squamous cell carcinoma are treated with chemoradiation as opposed to surgery (e.g., head and neck cancer and upper esophageal cancer).

Consequently, the definitive treatment paradigm for most non-metastatic squamous cell carcinomas employs chemoradiation or radiation alone.

The superiority of chemoradiation versus radiation alone was demonstrated by two large randomized prospective clinical trials [129, 130]. The United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) Anal Cancer Trial Working Party enrolled 585 patients to either radiation alone (45 Gy in 20 or 25 fractions) or chemoradiation (the same radiation dose with continuous infusion 5-FU plus bolus mitomycin C [MMC]) [131]. The 3-year local control rate was significantly longer in patients treated with chemoradiation (61 versus 36%, $p < 0.001$), though no difference was seen in OS. Similarly, researchers in Europe investigated the use of radiation alone (45 Gy in 25 fractions, with a boost at 6 weeks) versus chemoradiation (the same radiation dose and schedule with continuous infusion 5-FU and bolus mitomycin C) [129]. Both 5-year locoregional control (68 versus 50%, $p = 0.02$) and colostomy-free survival (72 versus 40%, $p = 0.002$) were improved with the addition of chemotherapy to the radiation. It is important to note that both trials used classical radiation techniques (3D-CRT).

The landmark trial that has served as the backbone for anal cancer, RTOG 98-11, was published by Ajani and colleagues in 2006 [132] and updated in 2012 [133]. Patients with T2–T4, N0–N3, and M0 anal squamous cell cancers were stratified to concurrent chemoradiation with mitomycin and 5-FU or induction 5-FU and cisplatin to be followed by concurrent 5-FU, cisplatin, and radiation. The radiation dose in all patients was 45 Gy if T2N0, or up to 55–59 Gy in T3, T4, node-positive, or T2 with residual disease. The induction nature of the cisplatin arm of this trial remains a controversial point. At 5 years, the mitomycin arm resulted in superior outcomes for colostomy-free survival (71.9 versus 65.0%, $p = 0.05$), DFS (67.8% versus 57.8%, $p = 0.006$), and OS (78.3 versus 70.7, $p = 0.026$). While the most significant treatment-related toxicity was hematologic (and resulted in most treatment delays), toxicity attributed to radiotherapy was significant, including radiation dermatitis and GI toxicity. As this trial utilized classical 3D-CRT techniques, these toxicities were not unexpected.

Intensity-Modulated Radiation Therapy in Anal Cancer

In order to improve the toxicity profile associated with 3D-CRT, the RTOG completed their prospective protocol 0529, an investigation of dose-painted IMRT (DP-IMRT) in T2-4, N0-3, M0 anal squamous cell carcinoma [134]. The term "dose-painted" refers to the ability of IMRT treatment fields to apply a more concentrated radiation dose into a small target volume within a larger target volume, and this is represented in Fig. 24.6. The investigators sought to determine whether or not the use of DP-IMRT with 5-FU and MMC chemotherapy resulted in a reduction of combined grade 2 or greater GI and genitourinary (GU) side effects by at least 15% when compared to the radiation/5FU/mitomycin C arm of RTOG 98-11. Radiation doses were 45 Gy to elective nodal regions, 50.4 Gy for lymph nodes ≤3 cm in size, and 54 Gy to lymph nodes greater than 3 cm in size and to the primary anal tumor (all in 30 fractions). The exception was patients with T2N0 lesions, who received 50.4 Gy to the anal tumor and 42 Gy to the elective nodal regions in 28 fractions.

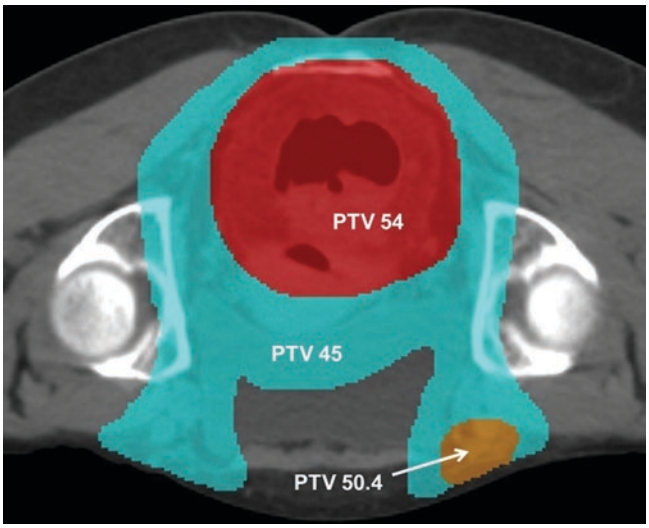


Fig. 24.6 Dose-painted intensity-modulated radiation therapy (DP-IMRT) target volumes and doses. A representative image of target volumes and doses in a cT3N3M0, stage IIIB case. The primary tumor planning target volume (PTV) receives 54 Gy (red colorwash) and the elective nodes 45 Gy (blue colorwash). An involved right-sided inguinal node was dose-painted to 50.4 Gy (orange colorwash). (Reprinted with permission from Kachnic et al. [134])

The primary endpoint of RTOG 0529, grade 2 or higher GI/GU toxicity, was not found to be superior using IMRT as opposed to 3D-CRT (77% versus 77%, $p = 0.50$). Therefore, based on the pre-determined criteria of the trial, RTOG 0529 was a negative trial. However, grade 3 or higher GI/GU toxicity was significantly lower using IMRT (21% versus 37%, $p = 0.0052$). Additionally, grade 3 or higher skin toxicity was much significantly decreased with IMRT (23 versus 49%, $p < 0.0001$). Equivalently as important, the use of smaller radiation fields with IMRT in RTOG 0529 did not increase the rate of local failure compared to 3D-CRT in RTOG 98-11. The 2-year local failure rate (20% versus 23%), colostomy-free survival (86% versus 84%), disease-free survival (77% versus 71%), and OS (88% versus 91%) were not statistically different between the trials. Treatment breaks during chemoradiation have been well documented to result

in inferior outcomes in patients with anal cancer [135]. Treatment interruptions, as noted by total duration of radiation, were significantly lower in patients treated with IMRT (treatment duration 43 days IMRT versus 49 days 3D-CRT, $p < 0.0001$). IMRT in anal cancer is, therefore, considered to maintain treatment efficacy while reducing acute morbidity compared to 3D-CRT.

At least two recent studies have utilized VMAT is a delivery method for IMRT in patients with anal cancer with promising results [136, 137]. A dosimetric comparison of ten patients comparing 7-field IMRT with VMAT was completed by investigators at MDACC [138]. Not only were VMAT plans more homogeneous than their IMRT counterparts (homogeneity index 2.4% VMAT versus 4.6% IMRT, $p = 0.007$), but also doses to multiple critical structures were significantly lower including the small bowel (mean dose 35.5 Gy IMRT versus 31.6 Gy VMAT, $p = 0.02$) and genitalia (mean dose 25.4 Gy IMRT versus 21.0 Gy VMAT, $p = 0.03$). Specifically for the small bowel, it was noted that while volume receiving low dose V10 Gy was higher with VMAT, the volume receiving intermediate dose V20 Gy was higher with IMRT. Finally, treatments were considerably faster with VMAT as opposed to IMRT (188 seconds versus 728 seconds, $p = 0.005$). Again, while an intriguing outcome, a direct clinical comparison between VMAT and IMRT in anal cancer remains lacking.

Charged Particle Therapy in Anal Cancer

Recently, two dosimetric studies have been published that investigate the ability of proton beam radiation to adequately treat anal cancer with less potential toxicity than IMRT [139, 140]. A radiation planning study from the University of Pennsylvania reported that a two-posterior oblique field proton beam plan showed reduced volumes of low and intermediate doses to many normal structures when compared to a 7-field IMRT plan [139]. Specifically, the small bowel volume irradiated was reduced using proton beam radiation for all doses up to 35 Gy with a minimum p-value of 0.0008. Similarly, proton beam radiation reduced the irradiated volume of external genitalia for all doses up to 29 Gy with a minimum p-value of 0.008.The mean external genitalia dose was 7.4 Gy with proton beam radiation and 19.4 Gy with IMRT ($p = 0.008$). Likewise, investigators from the Mayo Clinic demonstrated reduced volumetric doses for bone marrow, bladder, and small bowel normal structures [140]. As data emerges from anal cancer patients treated with proton beam radiation, the comparison in toxicities between proton beam radiation and IMRT/VMAT will inform the field about whether or not this dosimetric benefit is realized clinically.

Conclusion

The role of radiation remains paramount in most GI malignancies. As technology continues to advance, the role of radiation therapy will continue to evolve in turn. As with the progression from non-CT-based planning to SBRT, improvements in the delivery of proton beam therapy will likely help to reduce normal tissue toxicity while further dose-escalating the target. Consequently, previously radio-resistant tumors may be more meaningful therapeutic targets with high-dose radiation, and tumors once considered non-operable may be downstaged to allow for safe and effective surgical resection. Finally, as radiation dose is maximally increased and safe technique is further optimized, a future may be realized in which surgical management of certain tumors becomes unnecessary.

References

1. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991;21(1):109–22.
2. Kumar R, Wild AT, Ziegler MA, Hooker TK, Dah SD, Tran PT, et al. Stereotactic body radiation therapy planning with duodenal sparing using volumetric-modulated arc therapy vs intensity-modulated radiation therapy in locally advanced pancreatic cancer: a dosimetric analysis. Med Dosim. 2013;38(3):243–50.
3. Nabavizadeh N, Simeonova AO, Waller JG, Romer JL, Monaco DL, Elliott DA, et al. Volumetric-modulated arc radiotherapy for pancreatic malignancies: Dosimetric comparison with sliding-window intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy. Med Dosim. 2014;39(3):256–60.
4. Li Z, Zeng J, Wang Z, Zhu H, Wei Y. Dosimetric comparison of intensity modulated and volumetric arc radiation therapy for gastric cancer. Oncol Lett. 2014;8(4):1427–34.
5. Zhao J, Hu W, Cai G, Wang J, Xie J, Peng J, et al. Dosimetric comparisons of VMAT, IMRT and 3DCRT for locally advanced rectal cancer with simultaneous integrated boost. Oncotarget. 2016;7(5):6345–51.
6. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan clinical oncology group study JCOG0403. Int J Radiat Oncol Biol Phys. 2015;93(5):989–96.
7. Kuperman VY. Effect of radiation protraction on BED in the case of large fraction dose. Med Phys. 2013;40(8):081716.
8. Lievens Y, Pijls-Johannesma M. Health economic controversy and cost-effectiveness of proton therapy. Semin Radiat Oncol. 2013;23(2):134–41.
9. Sands SA. Proton beam radiation therapy: the future may prove brighter for pediatric patients with brain tumors. J Clin Oncol. 2016;34(10):1024–6.
10. Cai S, Hong TS, Goldberg SI, Fernandez-del Castillo C, Thayer SP, Ferrone CR, et al. Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978 to 2010. Cancer. 2013;119(23):4196–204.
11. Hyngstrom JR, Tzeng CW, Beddar S, Das P, Krishnan S, Delclos ME, et al. Intraoperative radiation therapy for locally advanced

primary and recurrent colorectal cancer: ten-year institutional experience. J Surg Oncol. 2014;109(7):652–8.
12. Roeder F, Ulrich A, Habl G, Uhl M, Saleh-Ebrahimi L, Huber PE, et al. Clinical phase I/II trial to investigate preoperative dose-escalated intensity-modulated radiation therapy (IMRT) and intraoperative radiation therapy (IORT) in patients with retroperitoneal soft tissue sarcoma: interim analysis. BMC Cancer. 2014;14:617.
13. Vermaas M, Nuyttens JJ, Ferenschild FT, Verhoef C, Eggermont AM, de Wilt JH. Reirradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients. Radiother Oncol. 2008;87(3):357–60.
14. Moningi S, Armour EP, Terezakis SA, Efron JE, Gearhart SL, Bivalacqua TJ, et al. High-dose-rate intraoperative radiation therapy: the nuts and bolts of starting a program. J Contemp Brachytherapy. 2014;6(1):99–105.
15. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326(24):1593–8.
16. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (radiation therapy oncology group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20(5):1167–74.
17. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26(7):1086–92.
18. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
19. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851–6.
20. Chandra A, Guerrero TM, Liu HH, Tucker SL, Liao Z, Wang X, et al. Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer. Radiother Oncol. 2005;77(3):247–53.
21. Kole TP, Aghayere O, Kwah J, Yorke ED, Goodman KA. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer. Int J Radiat Oncol Biol Phys. 2012;83(5):1580–6.
22. Lin SH, Wang L, Myles B, Thall PF, Hofstetter WL, Swisher SG, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2012;84(5):1078–85.
23. Welsh J, Gomez D, Palmer MB, Riley BA, Mayankkumar AV, Komaki R, et al. Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study. Int J Radiat Oncol Biol Phys. 2011;81(5):1336–42.
24. Akutsu Y, Yasuda S, Nagata M, Izumi Y, Okazumi S, Shimada H, et al. A phase I/II clinical trial of preoperative short-course carbon-ion radiotherapy for patients with squamous cell carcinoma of the esophagus. J Surg Oncol. 2012;105(8):750–5.
25. Muijs CT, Beukema JC, Pruim J, Mul VE, Groen H, Plukker JT, et al. A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer. Radiother Oncol. 2010;97(2):165–71.
26. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
27. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725–30.
28. Park SH, Sohn TS, Lee J, Lim DH, Hong ME, Kim KM, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol. 2015;33(28):3130–6.
29. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, Lind PA, Putter H, Jansen EP, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer. 2011;11:329–2407-11-329.
30. Minn AY, Hsu A, La T, Kunz P, Fisher GA, Ford JM, et al. Comparison of intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy as adjuvant therapy for gastric cancer. Cancer. 2010;116(16):3943–52.
31. Trip AK, Nijkamp J, van Tinteren H, Cats A, Boot H, Jansen EP, et al. IMRT limits nephrotoxicity after chemoradiotherapy for gastric cancer. Radiother Oncol. 2014;112(2):289–94.
32. Wang X, Li G, Zhang Y, Bai S, Xu F, Wei Y, et al. Single-arc volumetric-modulated arc therapy (sVMAT) as adjuvant treatment for gastric cancer: Dosimetric comparisons with three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT). Med Dosim. 2013;38(4):395–400.
33. Dionisi F, Avery S, Lukens JN, Ding X, Kralik J, Kirk M, et al. Proton therapy in adjuvant treatment of gastric cancer: planning comparison with advanced x-ray therapy and feasibility report. Acta Oncol. 2014;53(10):1312–20.
34. Koyama S, Kawanishi N, Fukutomi H, Osuga T, Iijima T, Tsujii H, et al. Advanced carcinoma of the stomach treated with definitive proton therapy. Am J Gastroenterol. 1990;85(4):443–7.
35. Shibuya S, Takase Y, Aoyagi H, Orii K, Sharma N, Tsujii H, et al. Definitive proton beam radiation therapy for inoperable gastric cancer: a report of two cases. Radiat Med. 1991;9(1):35–40.
36. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120(8):899–903.
37. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776–82; discussion 782-4.
38. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073–81.
39. Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol. 2010;28(29):4450–6.
40. Herman JM, Swartz MJ, Hsu CC, Winter J, Pawlik TM, Sugar E, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins hospital. J Clin Oncol. 2008;26(21):3503–10.

41. Corsini MM, Miller RC, Haddock MG, Donohue JH, Farnell MB, Nagorney DM, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). J Clin Oncol. 2008;26(21):3511–6.
42. Hsu CC, Herman JM, Corsini MM, Winter JM, Callister MD, Haddock MG, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. Ann Surg Oncol. 2010;17(4):981–90.
43. Goodman KA, Regine WF, Dawson LA, Ben-Josef E, Haustermans K, Bosch WR, et al. Radiation therapy oncology group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer. Int J Radiat Oncol Biol Phys. 2012;83(3):901–8.
44. no authors listed. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. J Natl Cancer Inst. 1988;80(10):751–5.
45. Faris JE, Blaszkowsky LS, McDermott S, Guimaraes AR, Szymonifka J, Huynh MA, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. Oncologist. 2013;18(5):543–8.
46. Loehrer PJ Sr, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an eastern cooperative oncology group trial. J Clin Oncol. 2011;29(31):4105–12.
47. Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: the Gastrointestinal Tumor Study Group. Cancer. 1981;48(8):1705–10.
48. Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, et al. LAP07 Trial Group. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. JAMA. 2016;315(17):1844–53.
49. Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010;7(4):e1000267.
50. Yovino S, Poppe M, Jabbour S, David V, Garofalo M, Pandya N, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. Int J Radiat Oncol Biol Phys. 2011;79(1):158–62.
51. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18(5):1319–26.
52. Ben-Josef E, Schipper M, Francis IR, Hadley S, Ten-Haken R, Lawrence T, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2012;84(5):1166–71.
53. Prasad S, Cambridge L, Huguet F, Chou JF, Zhang Z, Wu AJ, et al. Intensity modulated radiation therapy reduces gastrointestinal toxicity in locally advanced pancreas cancer. Pract Radiat Oncol. 2016;6(2):78–85.
54. Lee KJ, Yoon HI, Chung MJ, Park JY, Bang S, Park SW, et al. A comparison of gastrointestinal toxicities between intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for pancreatic cancer. Gut Liver. 2016;10(2):303–9.
55. Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol. 2009;27(11):1806–13.
56. Chapman KL, Witek ME, Chen H, Showalter TN, Bar-Ad V, Harrison AS. Pancreatic cancer planning: complex conformal vs modulated therapies. Med Dosim. 2016;41:100.
57. Ali AN, Dhabaan AH, Jarrio CS, Siddiqi AK, Landry JC. Dosimetric comparison of volumetric modulated arc therapy and intensity-modulated radiation therapy for pancreatic malignancies. Med Dosim. 2012;37(3):271–5.
58. Herman JM, Crane CH, Iacobuzio-Donahue C, Abrams RA. Pancreatic cancer. In: Gunderson LLTJ, editor. Clinical radiation oncology: expert consult. 4th ed: Elsevier; 2015. p. 934–59.
59. Kumar R, Rosati LM, Herman JM. Stereotactic body radiation therapy as an emerging option for localized pancreatic cancer. In: MHGAS K, editor. Multimodality management of borderline resectable and locally advanced pancreatic cancer: Springer; 2015.
60. Moningi S, Marciscano AE, Rosati LM, Ng SK, Teboh Forbang R, Jackson J, et al. Stereotactic body radiation therapy in pancreatic cancer: the new frontier. Expert Rev Anticancer Ther. 2014;14(12):1461–75.
61. Hoyer M, Roed H, Sengelov L, Traberg A, Ohlhuis L, Pedersen J, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiother Oncol. 2005;76(1):48–53.
62. Koong AC, Le QT, Ho A, Fong B, Fisher G, Cho C, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004;58(4):1017–21.
63. Schellenberg D, Goodman KA, Lee F, Chang S, Kuo T, Ford JM, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2008;72(3):678–86.
64. Schellenberg D, Kim J, Christman-Skieller C, Chun CL, Columbo LA, Ford JM, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2011;81(1):181–8.
65. Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2014; https://doi.org/10.1002/cncr.29161.
66. Mahadevan A, Jain S, Goldstein M, Miksad R, Pleskow D, Sawhney M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2010;78(3):735–42.
67. Polistina F, Costantin G, Casamassima F, Francescon P, Guglielmi R, Panizzoni G, et al. Unresectable locally advanced pancreatic cancer: a multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration. Ann Surg Oncol. 2010;17(8):2092–101.
68. Gurka MK, Collins SP, Slack R, Tse G, Charabaty A, Ley L, et al. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety. Radiat Oncol. 2013;8:44–717X-8-44.
69. Mellon EA, Hoffe SE, Springett GM, Frakes JM, Strom TJ, Hodul PJ, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. Acta Oncol. 2015;54(7):979–85.
70. Moningi S, Dholakia AS, Raman SP, Blackford A, Cameron JL, Le DT, et al. The role of stereotactic body radiation therapy for pancreatic cancer: a single-institution experience. Ann Surg Oncol. 2015;22(7):2352–8.
71. Lominska CE, Unger K, Nasr NM, Haddad N, Gagnon G. Stereotactic body radiation therapy for reirradiation of

localized adenocarcinoma of the pancreas. Radiat Oncol. 2012;7:74–717X-7-74.
72. Wild AT, Hiniker S, Chang DT, Tran PT, Khashab MA, Limaye MR, et al. Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions. J Gastrointest Oncol. 2013 Dec;4(4):343–51.
73. Dagoglu N, Callery M, Moser J, Tseng J, Kent T, Bullock A, et al. Stereotactic body radiotherapy (SBRT) reirradiation for recurrent pancreas cancer. J Cancer. 2016;7(3):283–8.
74. Hong TS, Ryan DP, Borger DR, Blaszkowsky LS, Yeap BY, Ancukiewicz M, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. Int J Radiat Oncol Biol Phys. 2014;89(4):830–8.
75. Nichols RC, Huh S, Li Z, Rutenberg M. Proton therapy for pancreatic cancer. World J Gastrointest Oncol. 2015;7(9):141–7.
76. Terashima K, Demizu Y, Hashimoto N, Jin D, Mima M, Fujii O, et al. A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. Radiother Oncol. 2012;103(1):25–31.
77. Takatori K, Terashima K, Yoshida R, Horai A, Satake S, Ose T, et al. Upper gastrointestinal complications associated with gemcitabine-concurrent proton radiotherapy for inoperable pancreatic cancer. J Gastroenterol. 2014;49(6):1074–80.
78. Ding X, Dionisi F, Tang S, Ingram M, Hung CY, Prionas E, et al. A comprehensive dosimetric study of pancreatic cancer treatment using three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated radiation therapy (VMAT), and passive-scattering and modulated-scanning proton therapy (PT). Med Dosim. 2014;39(2):139–45.
79. Thompson RF, Mayekar SU, Zhai H, Both S, Apisarnthanarax S, Metz JM, et al. A dosimetric comparison of proton and photon therapy in unresectable cancers of the head of pancreas. Med Phys. 2014;41(8):081711.
80. Santoro JP, Yorke E, Goodman KA, Mageras GS. From phase-based to displacement-based gating: a software tool to facilitate respiration-gated radiation treatment. J Appl Clin Med Phys. 2009;10(4):2982.
81. Schellenberg D, Quon A, Minn AY, Graves EE, Kunz P, Ford JM, et al. 18Fluorodeoxyglucose PET is prognostic of progression-free and overall survival in locally advanced pancreas cancer treated with stereotactic radiotherapy. Int J Radiat Oncol Biol Phys. 2010;77(5):1420–5.
82. Aitken KL, Hawkins MA. The role of radiotherapy and chemoradiation in the management of primary liver tumours. Clin Oncol (R Coll Radiol). 2014;26(9):569–80.
83. Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RK, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013;31(13):1631–9.
84. Klein J, Dawson LA, Jiang H, Kim J, Dinniwell R, Brierley J, et al. Prospective longitudinal assessment of quality of life for liver cancer patients treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys. 2015;93(1):16–25.
85. Brade AM, Ng S, Brierley J, Kim J, Dinniwell R, Ringash J, et al. Phase 1 trial of sorafenib and stereotactic body radiation therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2016;94(3):580–7.
86. Kimura T, Aikata H, Takahashi S, Takahashi I, Nishibuchi I, Doi Y, et al. Stereotactic body radiotherapy for patients with small hepatocellular carcinoma ineligible for resection or ablation therapies. Hepatol Res. 2015;45(4):378–86.
87. Crane CH, Koay EJ. Solutions that enable ablative radiotherapy for large liver tumors: fractionated dose painting, simultaneous integrated protection, motion management, and computed tomography image guidance. Cancer. 2016;122:1974.
88. Abe T, Saitoh J, Kobayashi D, Shibuya K, Koyama Y, Shimada H, et al. Dosimetric comparison of carbon ion radiotherapy and stereotactic body radiotherapy with photon beams for the treatment of hepatocellular carcinoma. Radiat Oncol. 2015;10:187.
89. Qi WX, Fu S, Zhang Q, Guo XM. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol. 2015;114(3):289–95.
90. Keane FK, Hong TS. Charged particle therapy for hepatocellular carcinoma: a commentary on a recently published meta-analysis. Ann Transl Med. 2015;3(22):365–5839.2015.12.36.
91. Gunther J, Krishnan S. The evolving evidence for the efficacy and safety of charged particle therapy for hepatocellular carcinoma-a commentary. Ann Transl Med. 2015;3(22):364–5839.2015.12.10.
92. Yamazaki H, Nakamura S, Suzuki G, Aibe N, Yoshida K. Superiority of charged particle therapy in treatment of hepatocellular carcinoma (regarding qi W.X. et al. charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis). Radiother Oncol. 2016;118(2):420.
93. Lanciano R, Lamond J, Yang J, Feng J, Arrigo S, Good M, et al. Stereotactic body radiation therapy for patients with heavily pretreated liver metastases and liver tumors. Front Oncol. 2012;2:23.
94. Osmundson EC, Wu Y, Luxton G, Bazan JG, Koong AC, Chang DT. Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. Int J Radiat Oncol Biol Phys. 2015;91(5):986–94.
95. Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. J Clin Oncol. 2016;34(3):219–26.
96. Autorino R, Mattiucci GC, Ardito F, Balducci M, Deodato F, Macchia G, et al. Radiochemotherapy with gemcitabine in unresectable extrahepatic cholangiocarcinoma: long-term results of a phase II study. Anticancer Res. 2016;36(2):737–40.
97. Ibarra RA, Rojas D, Snyder L, Yao M, Fabien J, Milano M, et al. Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors. Acta Oncol. 2012;51(5):575–83.
98. Kopek N, Holt MI, Hansen AT, Hoyer M. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. Radiother Oncol. 2010;94(1):47–52.
99. Barney BM, Olivier KR, Miller RC, Haddock MG. Clinical outcomes and toxicity using stereotactic body radiotherapy (SBRT) for advanced cholangiocarcinoma. Radiat Oncol. 2012;7:67–717X-7-67.
100. Polistina FA, Guglielmi R, Baiocchi C, Francescon P, Scalchi P, Febbraro A, et al. Chemoradiation treatment with gemcitabine plus stereotactic body radiotherapy for unresectable, non-metastatic, locally advanced hilar cholangiocarcinoma. Results of a five year experience. Radiother Oncol. 2011;99(2):120–3.
101. Makita C, Nakamura T, Takada A, Takayama K, Suzuki M, Ishikawa Y, et al. Clinical outcomes and toxicity of proton beam therapy for advanced cholangiocarcinoma. Radiat Oncol. 2014;9:26.
102. Ohkawa A, Mizumoto M, Ishikawa H, Abei M, Fukuda K, Hashimoto T, et al. Proton beam therapy for unresectable intrahepatic cholangiocarcinoma. J Gastroenterol Hepatol. 2015;30(5):957–63.
103. Hong TS, Wo JY, Yeap BY, Ben-Josef E, McDonnell EI, Blaszkowsky LS, et al. Multi-institutional phase II study of

high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2016;34(5):460–8.
104. Hoehn RS, Wima K, Ertel AE, Meier A, Ahmad SA, Shah SA, et al. Adjuvant therapy for gallbladder cancer: an analysis of the National Cancer Data Base. J Gastrointest Surg. 2015;19(10):1794–801.
105. Wang J, Narang AK, Sugar EA, Luber B, Rosati LM, Hsu CC, et al. Evaluation of adjuvant radiation therapy for resected gallbladder carcinoma: a multi-institutional experience. Ann Surg Oncol. 2015;22(Suppl 3):1100–6.
106. Ben-Josef E, Guthrie KA, El-Khoueiry AB, Corless CL, Zalupski MM, Lowy AM, et al. SWOG S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol. 2015;33(24):2617–22.
107. Mahadevan A, Dagoglu N, Tseng JF, Khawaja K, Evenson A. Therapeutic potential of adjuvant stereotactic body radiotherapy for gallbladder cancer. Cureus. 2015;7(8):e299.
108. Trial SRC, Cedermark B, Dahlberg M, Glimelius B, Påhlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980–7.
109. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638–46.
110. Jones WE 3rd, Thomas CR Jr, Herman JM, Abdel-Wahab M, Azad N, Blackstock W, et al. ACR appropriateness criteria® resectable rectal cancer. Radiat Oncol. 2012;7:161.
111. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet. 2001;358(9290):1291–304.
112. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40.
113. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the german CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926–33.
114. Arbea L, Ramos LI, Martinez-Monge R, Moreno M, Aristu J. Intensity-modulated radiation therapy (IMRT) vs. 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications. Radiat Oncol. 2010;5:17–717X-5-17.
115. Guerrero Urbano MT, Henrys AJ, Adams EJ, Norman AR, Bedford JL, Harrington KJ, et al. Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. Int J Radiat Oncol Biol Phys. 2006;65(3):907–16.
116. Tho LM, Glegg M, Paterson J, Yap C, MacLeod A, McCabe M, et al. Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer: investigating dose-volume relationships and role for inverse planning. Int J Radiat Oncol Biol Phys. 2006;66(2):505–13.
117. Samuelian JM, Callister MD, Ashman JB, Young-Fadok TM, Borad MJ, Gunderson LL. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2012;82(5):1981–7.
118. Wong SJ, Winter K, Meropol NJ, Anne PR, Kachnic L, Rashid A, et al. Radiation Therapy Oncology Group 0247: a randomized phase II study of neoadjuvant capecitabine and irinotecan or capecitabine and oxaliplatin with concurrent radiotherapy for patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2012;82(4):1367–75.
119. Hong TS, Moughan J, Garofalo MC, Bendell J, Berger AC, Oldenburg NB, et al. NRG oncology radiation therapy oncology group 0822: a phase 2 study of preoperative chemoradiation therapy using intensity modulated radiation therapy in combination with capecitabine and oxaliplatin for patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2015;93(1):29–36.
120. Tatsuzaki H, Urie MM, Willett CG. 3-D comparative study of proton vs. x-ray radiation therapy for rectal cancer. Int J Radiat Oncol Biol Phys. 1992;22(2):369–74.
121. Isacsson U, Montelius A, Jung B, Glimelius B. Comparative treatment planning between proton and X-ray therapy in locally advanced rectal cancer. Radiother Oncol. 1996;41(3):263–72.
122. Colaco RJ, Nichols RC, Huh S, Getman N, Ho MW, Li Z, et al. Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer. J Gastrointest Oncol. 2014;5(1):3–8.
123. Mokutani Y, Yamamoto H, Uemura M, Haraguchi N, Takahashi H, Nishimura J, et al. Effect of particle beam radiotherapy on locally recurrent rectal cancer: three case reports. Mol Clin Oncol. 2015;3(4):765–9.
124. Vuong T, Belliveau PJ, Michel RP, Moftah BA, Parent J, Trudel JL, et al. Conformal preoperative endorectal brachytherapy treatment for locally advanced rectal cancer: early results of a phase I/II study. Dis Colon Rectum. 2002;45(11):1486–93; discussion 1493-5.
125. Vuong T, Devic S, Podgorsak E. High dose rate endorectal brachytherapy as a neoadjuvant treatment for patients with resectable rectal cancer. Clin Oncol (R Coll Radiol). 2007;19(9):701–5.
126. Smith JA, Wild AT, Singhi A, Raman SP, Qiu H, Kumar R, et al. Clinicopathologic comparison of high-dose-rate endorectal brachytherapy versus conventional chemoradiotherapy in the neoadjuvant setting for resectable stages II and III low rectal cancer. Int J Surg Oncol. 2012;2012:406568.
127. Chuong MD, Fernandez DC, Shridhar R, Hoffe SE, Saini A, Hunt D, et al. High-dose-rate endorectal brachytherapy for locally advanced rectal cancer in previously irradiated patients. Brachytherapy. 2013;12(5):457–62.
128. Goodman KA, Patton CE, Fisher GA, Hoffe SE, Haddock MG, Parikh PJ, et al. Appropriate customization of radiation therapy for stage II and III rectal cancer: executive summary of an ASTRO clinical practice statement using the RAND/UCLA appropriateness method. Pract Radiat Oncol. 2016;6(3):166–75.
129. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the european organization for research and treatment of cancer radiotherapy and gastrointestinal cooperative groups. J Clin Oncol. 1997;15(5):2040–9.
130. no authors listed. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR anal cancer trial working party. UK Co-ordinating Committee on Cancer Research. Lancet. 1996;348(9034):1049–54.
131. Simoni M, Gromoll J. Monitoring the transfection efficiency of the human follicle-stimulating hormone receptor cDNA in COS-7 cells: evaluation of the growth hormone transient gene expression assay system. J Endocrinol Investig. 1996;19(6):359–64.
132. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB 3rd, Thomas CR Jr, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA. 2008;299(16):1914–21.

133. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB 3rd, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012;30(35):4344–51.
134. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys. 2013;86(1):27–33.
135. John M, Pajak T, Flam M, Hoffman J, Markoe A, Wolkov H, et al. Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92-08. Cancer J Sci Am. 1996;2(4):205–11.
136. Weber HE, Droge LH, Hennies S, Herrmann MK, Gaedcke J, Wolff HA. Volumetric intensity-modulated arc therapy vs. 3-dimensional conformal radiotherapy for primary chemoradiotherapy of anal carcinoma: effects on treatment-related side effects and survival. Strahlenther Onkol. 2015;191(11):827–34.
137. Capizzi PJ, Horton CE. A case of colonial gender conflict: Thomas (thomasine) hall. Ann Plast Surg. 1989;23(4):320–2.
138. Mok H, Briere TM, Martel MK, Beddar S, Delclos ME, Krishnan S, et al. Comparative analysis of volumetric modulated arc therapy versus intensity modulated radiation therapy for radiotherapy of anal carcinoma. Pract Radiat Oncol. 2011;1(3):163–72.
139. Anand A, Bues M, Rule WG, Keole SR, Beltran CJ, Yin J, et al. Scanning proton beam therapy reduces normal tissue exposure in pelvic radiotherapy for anal cancer. Radiother Oncol. 2015;117(3):505–8.
140. Ojerholm E, Kirk ML, Thompson RF, Zhai H, Metz JM, Both S, et al. Pencil-beam scanning proton therapy for anal cancer: a dosimetric comparison with intensity-modulated radiotherapy. Acta Oncol. 2015;54(8):1209–17.

Imaging in Gastrointestinal Cancers

25

Ali Devrim Karaosmanoglu, Mehmet Ruhi Onur, and Ronald S. Arellano

Introduction

Gastrointestinal (GI) cancers are among the leading health problems globally, and the burden is increasing in many parts of the world [1]. Imaging plays a crucial role in the diagnosis, follow-up, and screening of GI cancers. With the development of state-of-the-art technologies and increased experience with these modalities, imaging is generally the first diagnostic tool employed by physicians in modern medical practice.

In this chapter we provide a general overview of the common diagnostic imaging findings and optimal use of imaging technologies in the diagnosis, follow-up, and screening of gastrointestinal tract cancers.

Esophageal Cancer

General Overview

Esophageal carcinoma (EC) is the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide [2]. The survival rates are dismal, with overall 5-year survival ranges from 15% to 25%. The best outcomes are achieved with the disease diagnosed at an earlier stage [3, 4].

Squamous cell carcinoma is the most common histological subtype, with adenocarcinoma incidence rising dramatically in recent years [5, 6]. The clinical presentations tend to occur late in the course of EC, and therefore the patients are generally diagnosed at a later stage. The diagnosis is generally done by endoscopy, but as appropriate staging is crucial for the selection of optimal treatment approach in these patients, imaging plays a crucial role in the initial and follow-up staging.

The tumor can arise anywhere along the esophagus. As the esophagus lacks a proper serosal lining and attaches to neighboring structures via a loose adventitia, direct invasion of the adjacent structures may occur easily, including the thyroid, larynx, trachea, bronchi, aorta, lung, pericardium, diaphragm, and stomach. Tracheobronchial structures are commonly involved in the course of EC and, consequently, tracheoesophageal and esophagobronchial fistulas may develop in 5–10% of the cases [7]. Lymphatic dissemination of the EC is also common, and unpredictable, as there is extensive lymphatic network around the esophagus. The lymphatic drainage of the esophagus is rather longitudinal than segmental. The lymphatic metastases may develop distantly from the primary tumor, and abdominal lymph nodes may also be involved in 25–50% of the cases, more commonly from the distal ECs [8, 9]. Hematogenous metastases are also not infrequent and may involve the lungs, liver, bones, adrenal glands, pancreas, and kidney.

The diagnosis of EC is usually done with endoscopy. However, in some cases, conventional barium esophagogram may be the diagnostic study. On barium exam, the tumor may appear as an irregular, short segment stricture with proximal shouldering [10].

Role of Imaging in the Staging

Comprehensive work-up with endoscopic ultrasonography (EUS), computed tomography (CT)/magnetic resonance imaging (MRI), and positron emission tomography-CT (PET-CT) may all be required for staging of the EC.

A. D. Karaosmanoglu (✉) · M. R. Onur
Department of Radiology, Hacettepe University, School of Medicine, Sıhhiye, Ankara, Turkey

R. S. Arellano
Department of Radiology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_25

Endoscopic Ultrasonography

Endoscopic US is required for T staging of the tumor by determining the depth of the esophageal wall invasion by the tumor. High-frequency transducers are required as high morphologic detail is mandatory for invasion assessment. The differentiation of T1/T2 tumors from T3/T4 tumors is crucial as preoperative chemotherapy may be helpful before surgical resection in T3/T4 tumors; meanwhile surgical resection is preferred in T1/T2 tumors. Operator dependence, minimally invasive nature of the exam, suboptimal evaluation of the stenotic tumors, and perforation risk are the main limitations of the study [11].

Computed Tomography

Computed tomography exam is typically performed in the pre-surgical evaluation of the patients with known EC (Fig. 25.1a–c). Multidetector computed tomography (MDCT) is extremely useful to assess the tumor size, local invasion, lymph node involvement, and distant metastases. CT has been demonstrated to be highly accurate in the detection of local invasion of the adjacent structures such as the trachea, thoracic aorta, bronchus, or the pericardium (T4 tumor). The main diagnostic criterion for invasion is the loss of detectable fat planes between the esophagus and the invaded mediastinal structures. The displacement and indentation of the adjacent structures may be seen in cases of local invasion. The prediction of thoracic aortic invasion by the EC may be extremely difficult as there is no intervening fat plane between the esophagus and the aortic wall. If there is more than 90° of direct contact with the tumor and the aortic wall, then the tumor is deemed to be invading the aorta. In case the contact angle is between 45° and 90°, then the findings are considered to be indeterminate for aortic invasion. In cases where the contact is less than 45°, then there is no evidence of aortic wall invasion [12]. The sensitivity and specificity of CT for the detection of T3 and T4 diseases are 75%/78% and 75%/86%, respectively [13]. With the widespread use of MDCT, several multiplanar reformations may be done, which may allow better assessment of the length and anatomic relations of the EC.

CT is also a reliable tool for diagnosing the metastatic lymph node involvement. It can detect the enlarged lymph nodes and has sensitivity and specificity of 30–60% and 60–80%, respectively, for nodes greater than 1 cm [4, 14,

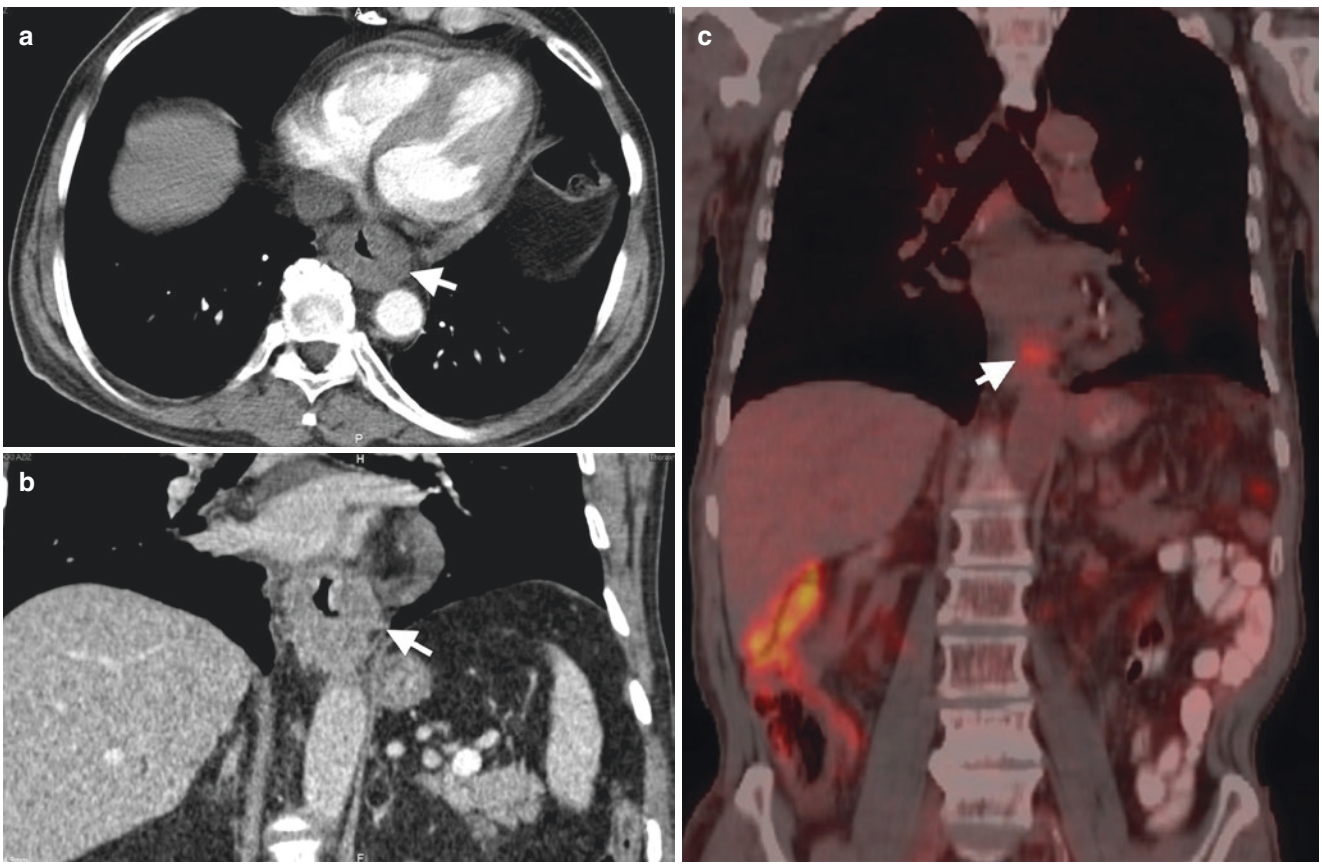


Fig. 25.1 Esophageal carcinoma. Axial (**a**) and coronal (**b**) contrast-enhanced CT images of a 60-year-old male demonstrate squamous cell carcinoma of the distal esophagus manifesting as concentric and asymmetric wall thickening (arrows). (**c**) Coronal PET-CT reveals increased FDG uptake (arrow) in the esophagus cancer

15]. Contrast-enhanced CT is also highly successful for the assessment of solid organ metastases.

Positron Emission Tomography-Computed Tomography

Esophagus cancer appears on PET-CT as increased 18F-fluorodeoxyglucose (18F-FDG) uptake (Fig. 25.1c). However, PET-CT is not used for primary detection or local staging of EC, but it is extremely useful for detection of distant solid organ and lymph node metastases.

Accurate diagnosis of lymph node metastasis is of crucial importance for the management of patients with known EC. The esophagus has an extensive lymphatic drainage, with most of the lymphatic channels from the upper two-thirds draining into the upper mediastinum, while the lower third mostly drains into the lower mediastinum and the abdomen [14]. However, due to the presence of extensive connections and collateral draining, it is not unusual to detect skip metastasis beyond the adjacent lymph nodes. Despite its success in the detection of the distant lymph node metastases, PET-CT has a low sensitivity and specificity (51% and 84%, respectively) in the local lymph node involvement as these nodes are often obscured by the intense metabolic activity in the primary tumor [16]. Solid organs are also commonly involved, with the lung and the liver being the most commonly affected ones; PET-CT is also successful in the detection of solid organ involvement [17].

Despite some conflicting results in several studies, it has been proposed that PET-CT also can be used as a prognostic indicator for the assessment of tumor response [11, 18, 19].

Gastric Cancer

General Overview

Gastric adenocarcinoma (GAC) is a common malignancy listed as the fourth most common cancer worldwide and as the second most common cause of cancer-related death worldwide [20]. The GAC rates increase with advancing age, and the majority of patients are diagnosed between the ages of 50–70. The highest incidence rates are in Asia (particularly the Far East countries including Japan, China, and Korea). The early stage at the time of detection makes the long-term survival highly favorable. Unfortunately, the symptoms of GAC are highly non-specific, and most patients get diagnosed with locally advanced or metastatic disease. The overall survival rates are poor with an estimated 5-year survival less than 20% [21, 22]. The rates of GAC are on the decline in the developed parts of the world over the past 50 years. Effective treatments against *Helicobacter pylori* infection and increased screening in Japan have accounted for the decrease.

The morphologic appearances of GAC differ widely and may present as asymmetric wall thickening, concentric mural mass, or diffuse gastric wall thickening with associated contraction, also known as linitis plastica. Gastric outlet obstruction presenting with unrelenting vomiting and significant abdominal distension may also be seen in antrally located tumors.

Role of Imaging in the Diagnosis and Staging

Accurate staging—both at the time of initial diagnosis and in between the chemotherapy cycles—is of crucial importance in selecting the correct treatment options for the affected patients. Endoscopy is the mainstay of definitive histopathologic diagnosis, and imaging is the main noninvasive tool for the detection of lymph node and solid organ involvement in the course of the disease.

Computed Tomography

Gastric cancer presents with asymmetric thickening of the gastric wall on CT (Fig. 25.2). Linitis plastica appears as diffuse gastric wall thickening (Fig. 25.3a–c). CT is the workhorse modality for differentiating the patients with locoregional disease from those with systemic disease. This stratification is crucial as patients with systemic disease are candidates for palliative treatment rather than aggressive surgical and medical oncologic interventions. Patients with locoregional disease need further staging based on whether they are candidates for surgical treatment or aggressive medical intervention.

Patients generally have a CT study early in the course of the disease, and those with detected visceral organ metastases may be precluded from unnecessary laparotomy.

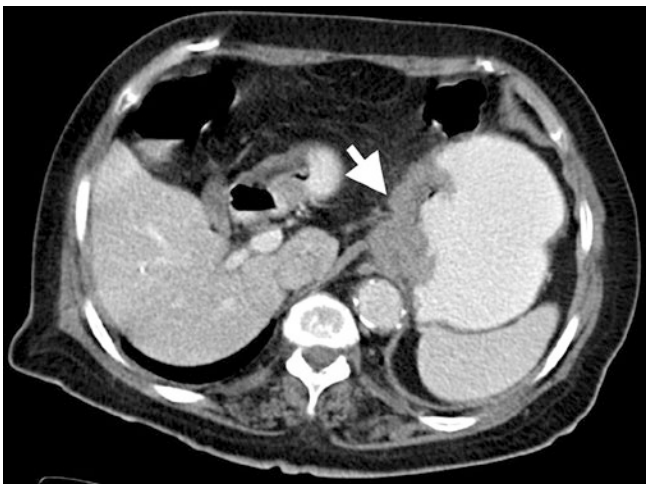


Fig. 25.2 Gastric adenocarcinoma. Axial contrast-enhanced CT image of a 72-year-old female demonstrates marked wall thickening in the cardia extending to lesser curvature (white arrow)

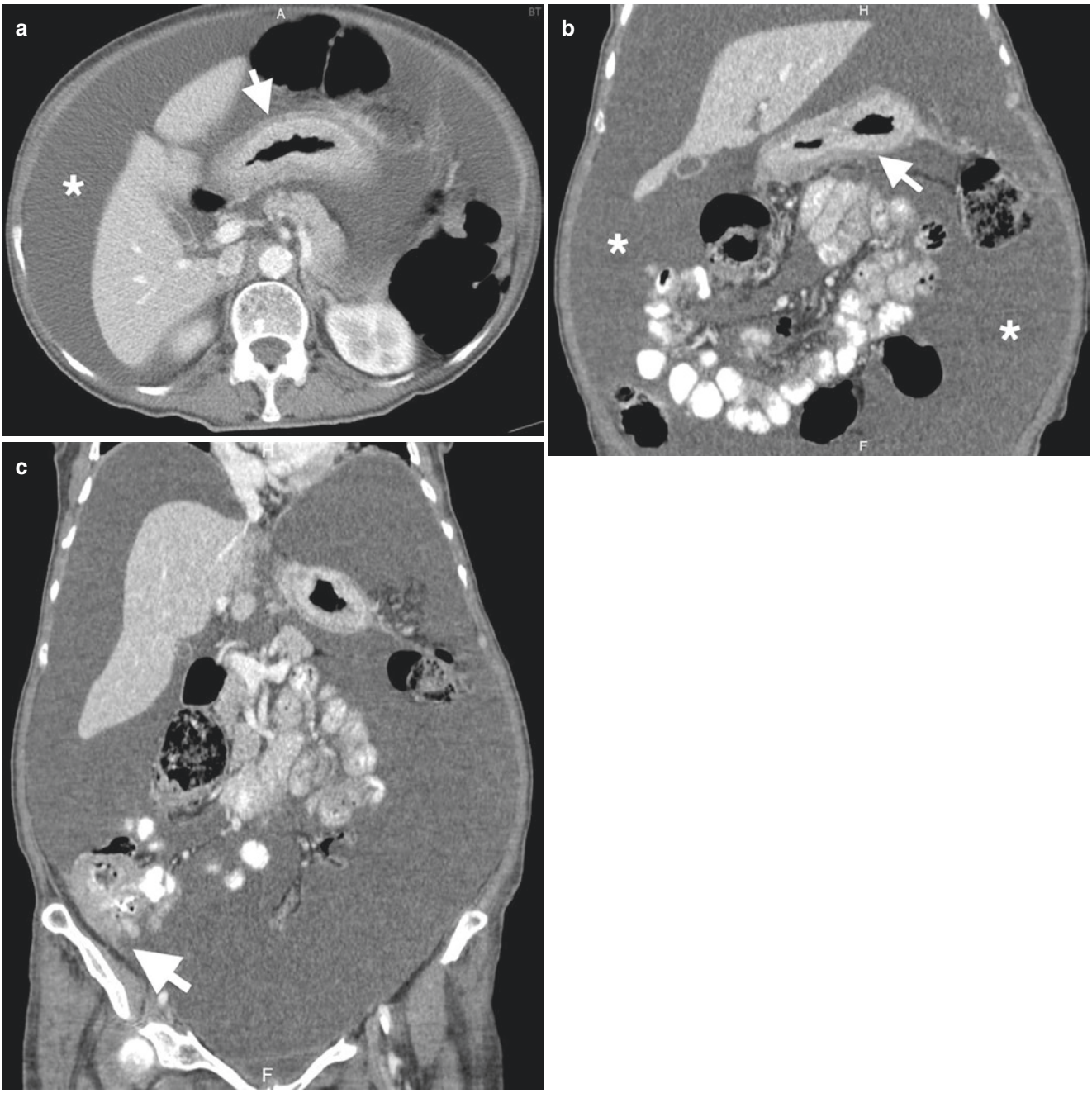


Fig. 25.3 Linitis plastica. (**a**) Axial and (**b**) coronal contrast-enhanced CT images of a 71-year-old woman with gastric adenocarcinoma. The tumor manifests as diffuse gastric wall thickening (arrow) with associated ascites (∗). (**c**) Coronal contrast-enhanced CT reveals tumoral implants (arrow) adjacent to the cecum

Peritoneal involvement is not unusual in the course of the disease, and CT may also be very sensitive in the early detection of ascites and peritoneal implants. Even in the absence of detectable peritoneal implants, the presence of ascites is a very strong indicator of peritoneal carcinomatosis, a poor prognostic finding, and CT is extremely sensitive even if the ascites is minute. The primary disease may or may not be detected with CT depending on the size of the disease. The main limitation of CT is relative insensitivity of detecting peritoneal and liver metastases smaller than 5 mm [23]. Lymph node classification is also mainly dependent on the size, which may cause false-negative interpretation.

Lymphomatous involvement of the GI tract most frequently occurs in the stomach. Gastric lymphoma may manifest as diffuse infiltration of the gastric wall, segmental infiltration, or localized polypoid form (Fig. 25.4a, b).

Gastrointestinal stromal tumors (GISTs) of the stomach mostly appear as a large, hypervascular, enhancing masses

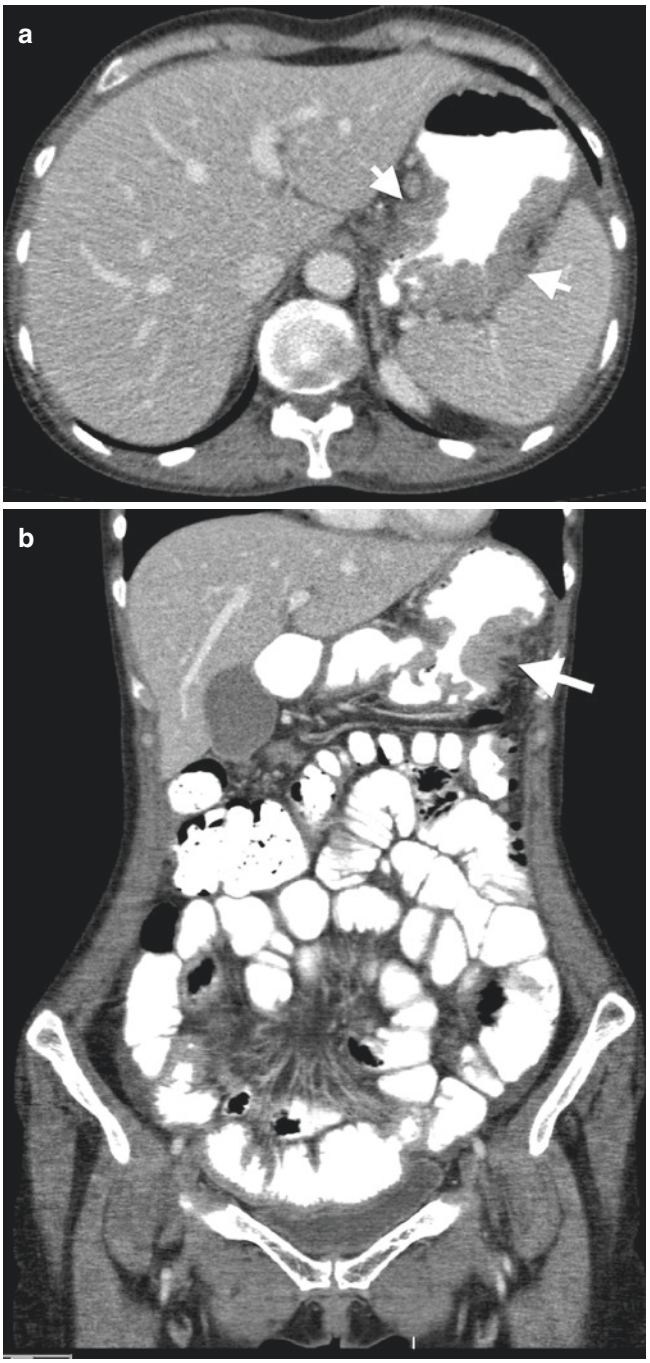


Fig. 25.4 Gastric lymphoma. Axial (**a**) and coronal (**b**) contrast-enhanced CT images of a 55-year-old female demonstrate mass-like thickening of the gastric wall with extension into the lumen (arrows)

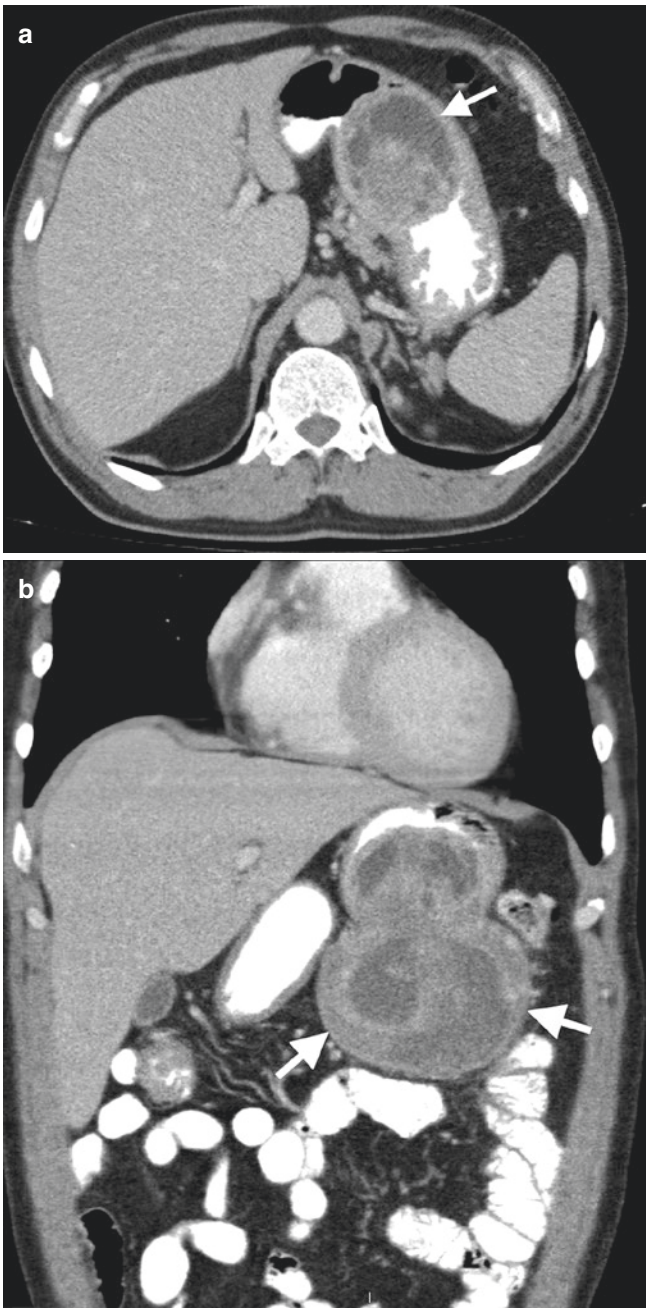


Fig. 25.5 Gastric gastrointestinal stromal tumor (GIST). Axial (**a**) and coronal (**b**) contrast-enhanced CT images demonstrate a lobulated, heterogeneous solid mass (arrows) arising from the gastric wall. The mass extends into the lumen and the perigastric fat planes

on contrast-enhanced CT. GIST of the stomach may be dumbbell-shaped due to exophytic growth pattern (Fig. 25.5a, b).

Magnetic Resonance Imaging

The use of MRI for the primary diagnosis of GAC is fairly uncommon. There are several impediments of using MRI in the diagnosis of gastric cancers. Several patient- and technique-related factors contribute to this limitation. Claustrophobia, inability to lie supine for an extended period of time, and the presence of cardiac pacemakers and other MR-unsafe body prostheses are the main patient factors. The peristalsis of the stomach, the presence of endoluminal gas, and the respiratory motion of the anterior abdominal wall may be counted among the technique-related difficulties

[24]. Small lesion size and lack of adequate distension of the stomach are among the other setbacks that may preclude the detection of small-sized gastric mural lesions.

Gastric cancers may be visualized as asymmetrically or mass-forming wall thickening on MRI (Fig. 25.6). Despite the aforementioned deterrents of the use of MRI for the diagnosis of the primary disease, MRI is very sensitive in the detection of hepatic and other visceral metastases. The introduction of diffusion-weighted imaging (DWI) and hepatocyte-specific MR contrast agents have great potential in early detection and characterization of the visceral metastatic disease.

Positron Emission Tomography-Computed Tomography

There is a growing use of PET-CT in the staging of the patients with GAC. Recently, several studies have been published with regard to the potential value of PET-CT in GAC staging [25, 26]. PET-CT has a similar sensitivity to CT (93%) for the detection of gastric cancer [27, 28]. The FDG uptake is lower in mucinous and signet ring cell tumors (standardized uptake value [SUV] mean, 4.2) which is directly linked to the lower expression of glucose transporter 1 (GLUT-1) on the cell surface, decreased cellularity, and increased amount of intracellular mucin in mucinous and signet ring cell tumors [27, 29, 30].

PET-CT may be helpful in the evaluation of lymph node involvement. Lymph nodes that are commonly affected are perigastric lymph nodes, but several regional nodal stations including the celiac artery and its branch vessels may also be detected. Unnecessary laparotomies may be prevented owing to the high specificity of PET-CT in cases of unresectable lymph node metastases [25]. Another common use of PET-CT is the detection of distant solid organ metastases from GAC. The liver, adrenals, kidneys, supraclavicular lymph nodes, ovaries, and spleen may all be involved [31]. Despite all efforts, it is well-known that more than half of the patients recur [32, 33]. PET-CT may be used in the detection of recurrence (Fig. 25.7a, b). The pattern of recurrence is systemic rather than local. The liver and the peritoneal cavity are the most common sites for systemic recurrence, whereas for local recurrences the most common sites are the resection margin, gastric bed, and the locoregional lymph nodes [34].

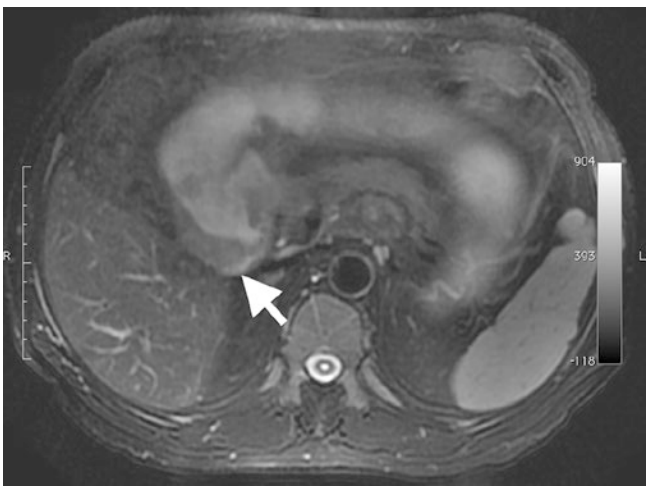


Fig. 25.6 Gastric adenocarcinoma. T2-weighted fat-saturated MR image demonstrates asymmetric hypointense wall thickening (arrow)

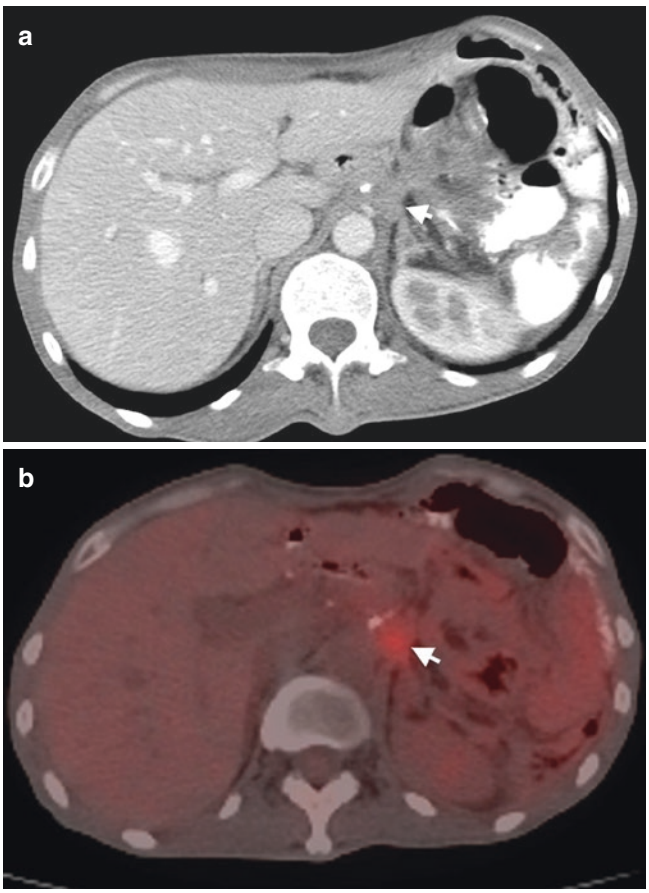


Fig. 25.7 Gastric carcinoma. (**a**) Axial contrast-enhanced CT image reveals a soft tissue mass (arrow) in the gastric remnant in a patient who is status post-partial gastrectomy. (**b**) PET-CT shows increased FDG uptake (arrow), consistent with recurrent tumor

Malignant Diseases of the Peritoneum

Brief Review of Peritoneal Anatomy and Physiology

Peritoneum is the serous membrane lining the abdominal cavity. The primary function of the peritoneum is to suspend the abdominal solid organs as well as the intestinal segments. In addition to its primary function, it also serves as a conduit for lymphovascular and neural networks that supply the

abdominal structures. Peritoneum may be affected by primary and secondary neoplastic diseases, with the secondary cancers being the most common. The complex anatomic structure of the peritoneum also allows the spread of malignant diseases to several abdominal compartments, sometimes in an unpredictable fashion. The prognosis and treatment of different neoplastic processes highly vary, and therefore, correct identification and reporting of the disease burden is of crucial importance for guiding the medical and surgical management and also is directly linked with successful outcomes. A multimodality approach to peritoneal imaging brings together the strength of each modality with the potential of increasing diagnostic accuracy. The peritoneum is composed of two layers, and the peritoneal cavity is the potential space between these two layers. The parietal peritoneum lines the abdominal wall, and the visceral peritoneum envelops the abdominal viscera. There is a very small volume of fluid within the peritoneal cavity with a content similar to plasma. Cephalic movement of the peritoneal fluid is caused by the negative intra-abdominal pressure during the respiration and also by the peristaltic movement of the intestinal segments.

General Overview

Peritoneal carcinomatosis (PC) is much more common than primary peritoneal neoplasms. Peritoneal spread of malignancy is generally a poor prognostic sign of advanced malignant disease. Most current surgical and pharmacological approaches to the treatment of PC are palliative. Several mechanisms of tumor dissemination to the peritoneum have been proposed, including seeding of the peritoneum by the dropped tumor cells as well as the hematogenous and lymphatic spread.

Intraperitoneal seeding mostly happens in the course of gastrointestinal and ovarian tumors. Secondary seeding has also been proposed as a consequence of surgery or biopsy when there is spillage of the tumor cells into the peritoneal cavity. Once the tumor cells gain access to the peritoneal cavity, the neoplastic cells adhere to the mesothelial lining of the peritoneum and infiltrate the submesothelial anatomic structures [35]. Once in the peritoneal cavity, the freely floating tumor cells also migrate with the peritoneal fluid and disseminate to several compartments of the abdomen. Hematogenous spread most commonly occurs in the setting of advanced stage disease and is most commonly detected with the primary tumors of the lung, breast, and melanoma [36].

PC may present with focal or diffuse disease. The diffuse type mainly presents in three different forms: (1) the plaque pattern, (2) the nodular implant pattern, and (3) the mass-like pattern [37]. The presentation of PC is highly variable, but most patients are asymptomatic or minimally symptomatic until the advanced stages of the disease. Abdominal distension, pain, bloating, and intestinal obstruction are common symptoms.

Peritoneal involvement can be seen in many subtypes of lymphoma and most frequently in diffuse large B-cell lymphoma. Omental involvement in the course of lymphomas is uncommon due to absence of lymphoid tissue in omentum.

Imaging of Peritoneal Carcinomatosis

CT, US, or MRI may all be used in the diagnosis and follow-up of PC, with CT and MRI being more common than US. US is very useful in the detection of ascites and also to a certain extent for the peritoneal masses when ascites is present [38]. However, it is an operator-dependent study, and in case of small volumes of ascites, its sensitivity may even drop further. PET-CT also has a role in the follow-up but is rarely used for the diagnosis of PC as the first-line modality.

Computed Tomography

CT is the unquestionable imaging modality for the diagnosis and follow-up of patients with PC. Choosing the relevant CT protocol and proper patient preparation are mandatory for optimal success with CT. Oral and intravenous (IV) contrast administration and rectal contrast use in some cases are crucial for success. The detection rate for implants is high with CT; with larger implants, the success rate is even higher [37]. With the advance of the MDCT technology, isotropic images may be reconstructed in any plane without any loss of information in the imaging data. The most common imaging findings of PC are nodular thickening and enhancement of the peritoneal lining with associated ascites. It is not uncommon to see displacement of the bowel loops and intestinal obstruction in advanced cases. With infiltration of the small bowel mesentery, the mesentery becomes stiff and loses its characteristic undulation. Perivascular spaces may also appear infiltrated, and this appearance may give rise to the so-called stellate mesentery [39–42].

As ascites is a common finding in the course of PC, the discovery of new-onset ascites should prompt a careful search for findings that may suggest peritoneal malignancy (Fig. 25.8a–c). In the absence of ascites, the detection of peritoneal implants may be quite challenging. In these cases, paracolic gutters, retrovesical space, ileocecal region, root of the small bowel mesentery, the pouch of Douglas, and subhepatic spaces should be scrutinized for occult metastatic disease [40] (Fig. 25.8a–c). It should also be borne in mind that mucinous carcinomatosis and pseudomyxoma peritonei may present as low attenuation masses on CT; and, in case of pseudomyxoma peritonei, loculated low attenuation masses may indent the contours of solid intra-abdominal organs.

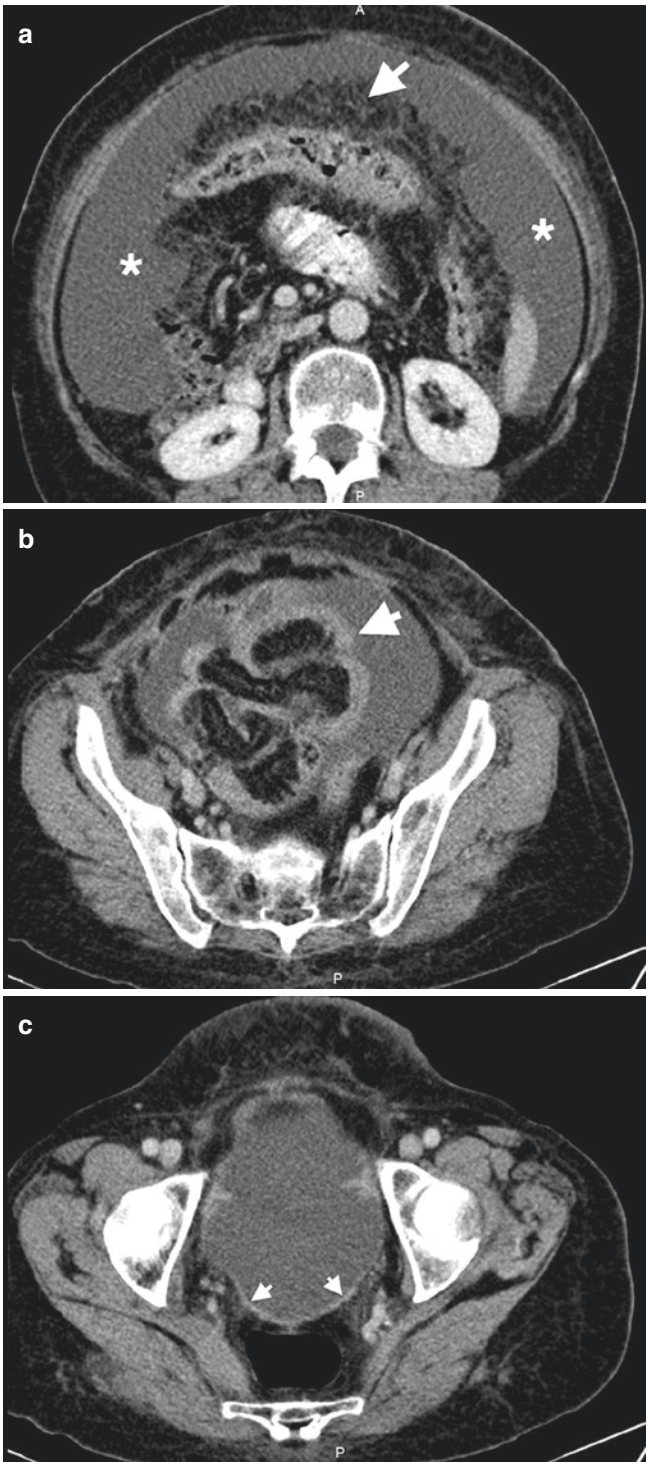


Fig. 25.8 Peritoneal carcinomatosis. (**a**) Axial contrast-enhanced CT image of a 71-year-old female reveals subtle nodularity of the greater omentum (arrow) consistent with peritoneal tumor infiltration. Massive ascites (∗). (**b**) Axial contrast-enhanced CT image demonstrates avid enhancement of serosal surfaces of the small bowel (arrow) indicating serosal tumor involvement. (**c**) Parietal peritoneum in pelvic region enhances (arrowheads) consistent with malignant infiltration

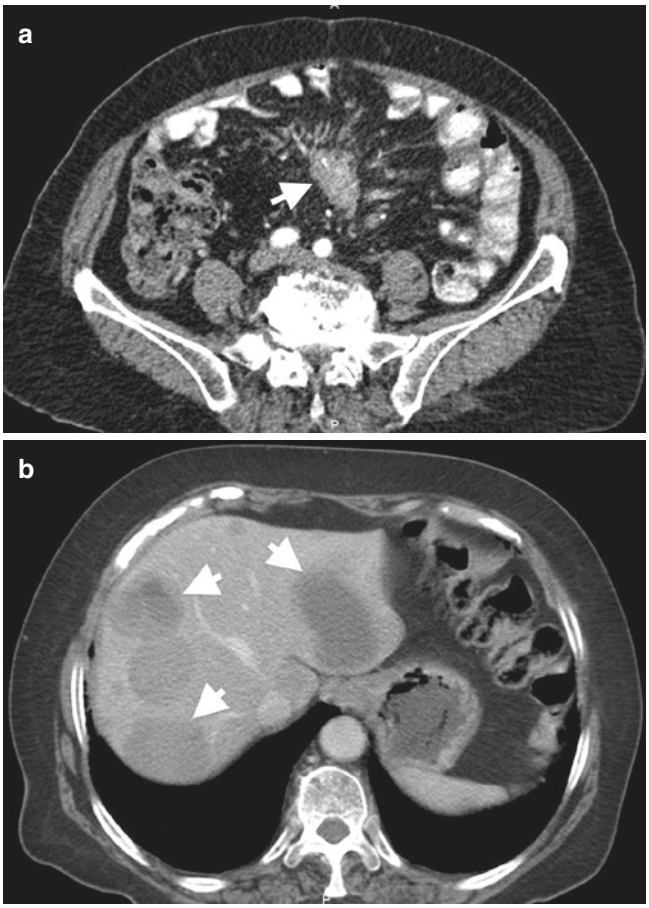


Fig. 25.9 Mesenteric carcinoid tumor. (**a**) Axial contrast-enhanced CT of a 74-year-old female shows a soft tissue mesenteric mass with subtle calcifications (arrow). (**b**) Low-attenuating focal hepatic lesions (arrows) consistent with metastatic disease from mesenteric carcinoid tumor

Mesenteric carcinoids present with the appearance of contrast-enhanced mass with linear bands radiating in the mesenteric fat on CT (Fig. 25.9a, b). Calcification can be detected in 70% of patients [39]. Accompanying fibrosis in the mesentery may create a "sunburst" or "spoke-wheel" pattern [39–40].

Peritoneal involvement of lymphoma may appear as visceral and parietal peritoneum thickening, omental mass, mesenteric mass, and bowel wall thickening. Visceral organ involvement, lymphadenopathies, and ascites may accompany the findings (Fig. 25.10a–e).

Magnetic Resonance Imaging

MDCT technology provides radiologists with high-resolution images in a very short time. However, the contrast resolution of CT may limit the detection of subtle peritoneal disease

and therefore to a select subgroup of patients. In a similar way, T2-weighted and non-contrast T1-weighted images of MRI also have limited use in detecting small peritoneal tumor deposits. Therefore, selection of adequate sequences and proper patient preparation are of crucial importance for an optimal MR study. Fat suppression and IV contrast use are mandatory for an optimal MR study performed for the evaluation of the peritoneum. Images of the peritoneal surfaces can be performed in several planes in order to mitigate the detection of the peritoneal nodules and enhancement. As peritoneal tumors tend to slowly uptake the IV-administered gadolinium and become more conspicuous on delayed images, image acquisition at this phase is mandatory. With its excellent high soft tissue contrast, MRI, especially with IV gadolinium administration, provides excellent images of the peritoneum and may allow the detection of CT occult peritoneal disease.

Positron Emission Tomography-Computed Tomography

Anatomic imaging with cross-sectional imaging modalities are the mainstay of peritoneal tumor implants; however, small nodules may be difficult to detect with CT and MRI. In some cases, PET-CT may provide diagnostic improvement [43]. The implants may appear as FDG-avid nodular soft tissue masses (Fig. 25.10e). Diffuse peritoneal FDG uptake is

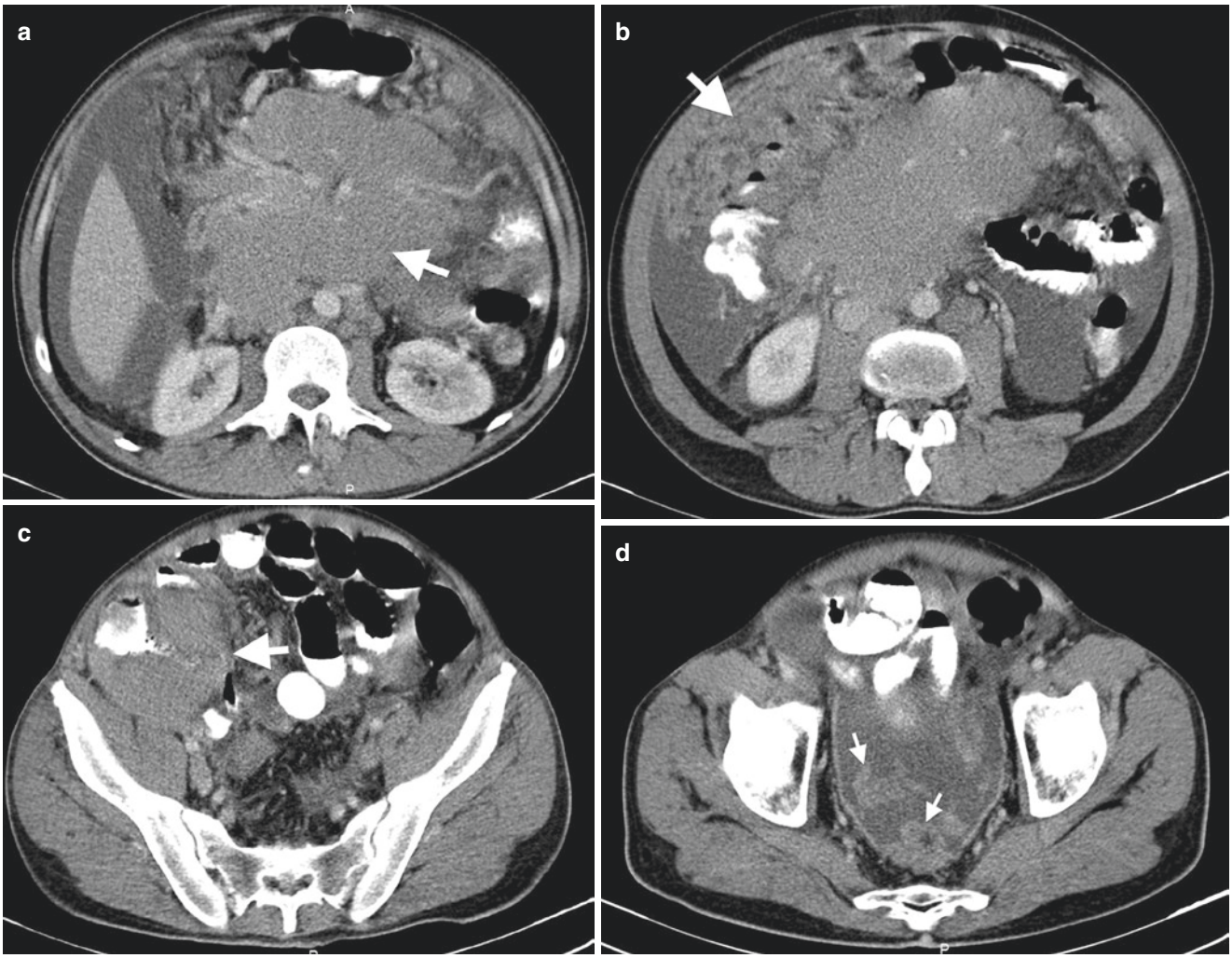


Fig. 25.10 Lymphomatous involvement in the peritoneum. (**a**) Axial contrast-enhanced CT of a 41-year-old male shows enlarged retroperitoneal lymph nodes manifesting as a bulky soft tissue mass (arrow). (**b**) Peritoneal lymphomatous involvement may present as omental cake (arrow). (**c**) Axial contrast-enhanced CT image demonstrates thickening of the cecal wall (arrow) consistent with lymphomatous involvement. (**d**) Axial contrast-enhanced CT demonstrates nodular masses in the pelvic parietal peritoneum (arrow) and lymphomatous involvement. (**e**) PET-CT shows increased FDG uptake (arrows) in peritoneal lymphomatous disease

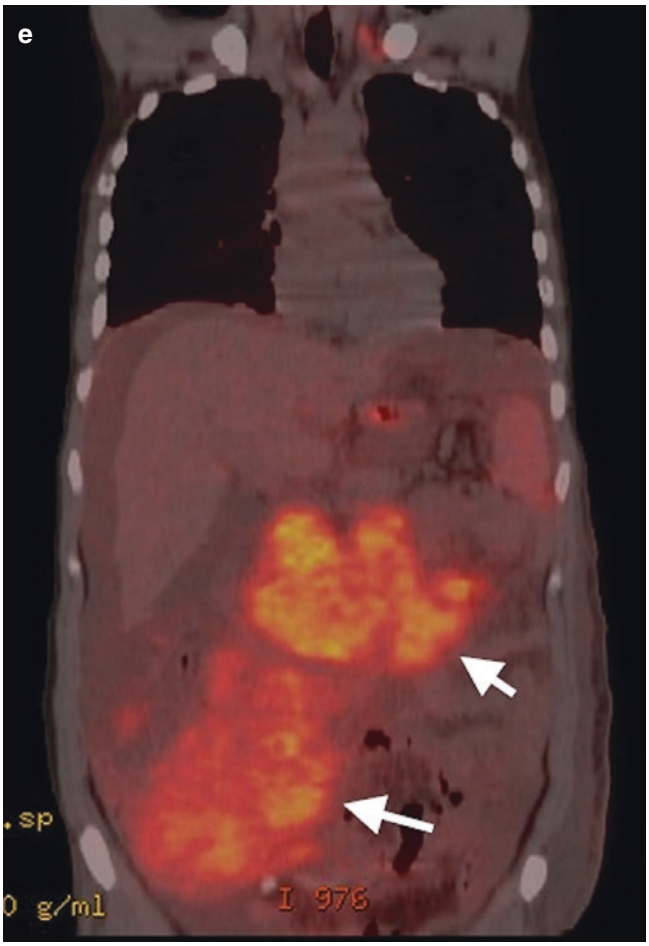


Fig. 25.10 (continued)

also an important sign of peritoneal malignant infiltration in the absence of discrete nodular peritoneal implants [43, 44]. PET-CT may have a significant potential for improving the decision-making process regarding surgical and medical treatment. It can also provide important information for monitoring response to therapy with its unique functional assessment feature in addition to anatomic evaluation.

Malignant Disease of the Small Bowel

General Overview

Primary tumors of the small bowel are rare. The most commonly encountered malignant lesions are adenocarcinomas, neuroendocrine tumors, and soft tissue sarcomas. Adenocarcinoma is the most common malignant neoplasm of the small bowel and accounts for 40% of all malignant small bowel neoplasms. The duodenum is the most common location followed by the jejunum and ileum [45]. The incidence of malignant small bowel neoplasms appear to be higher in North America and Western parts of Europe compared to Asia [46]. They are predominantly detected in older age groups and the mean age of presentation is 65. Sarcomas and lymphomas present earlier than the adenocarcinomas and carcinoid tumors. The incidence for all subtypes tends to increase after the age 40 [47, 48]. Metastatic disease to the small bowel is not infrequent, with breast, lung, and melanoma being the most common primaries [49].

Imaging is crucial for treatment planning as surgical resection is the only available curative treatment approach, except for small bowel lymphoma. Proper local staging and assessment of the distant metastases are crucial for optimal treatment planning. Barium studies with fluoroscopy were the main tool for the diagnosis in the past, but with the advance of endoscopic approaches, these studies have fallen out of favor. However, it may still play an important role in the diagnosis of cancer in distal small bowel segments (including ileal and jejunal). Other imaging modalities—including CT, MRI, and PET-CT—may all be used for the diagnosis and follow-up with CT being the workhorse modality.

Role of Imaging in Diagnosis and Follow-Up

Computed Tomography

Adequate distension of the small bowel lumen is crucial for the CT detection of the enteric lesions, and several agents have been proposed for providing endoluminal contrast. Oral contrast can be administered via oral route, intestinal tube, or simultaneous use of both routes. Each has its own pros and cons. The use of ordinary tap water as the endoluminal contrast is the most commonly employed technique. The administration of oral granules that release carbon dioxide may also be used in selected patients to obtain better intestinal distension. The use of IV contrast is also essential both for the evaluation of the primary mass and the metastatic burden of the disease.

The presence of concentric thickening of the mucosa is the most common imaging finding of adenocarcinomas with avid enhancement after IV contrast injection (Fig. 25.11a–d). Adenocarcinomas tend to grow endoluminally, but extension into the adjacent mesentery is not uncommon. In contrast to adenocarcinomas, gastrointestinal stromal tumors (GISTs) tend to grow toward the outside of the bowel lumen, which may provide a diagnostic clue for the correct diagnosis. The acquisition of early arterial phase images may also provide important diagnostic data regarding the presence/absence of vessel invasion as well as the detection of the necrotic areas in the tumor mass. Portal venous phase images are crucial for the evaluation of the liver parenchyma for metastatic disease.

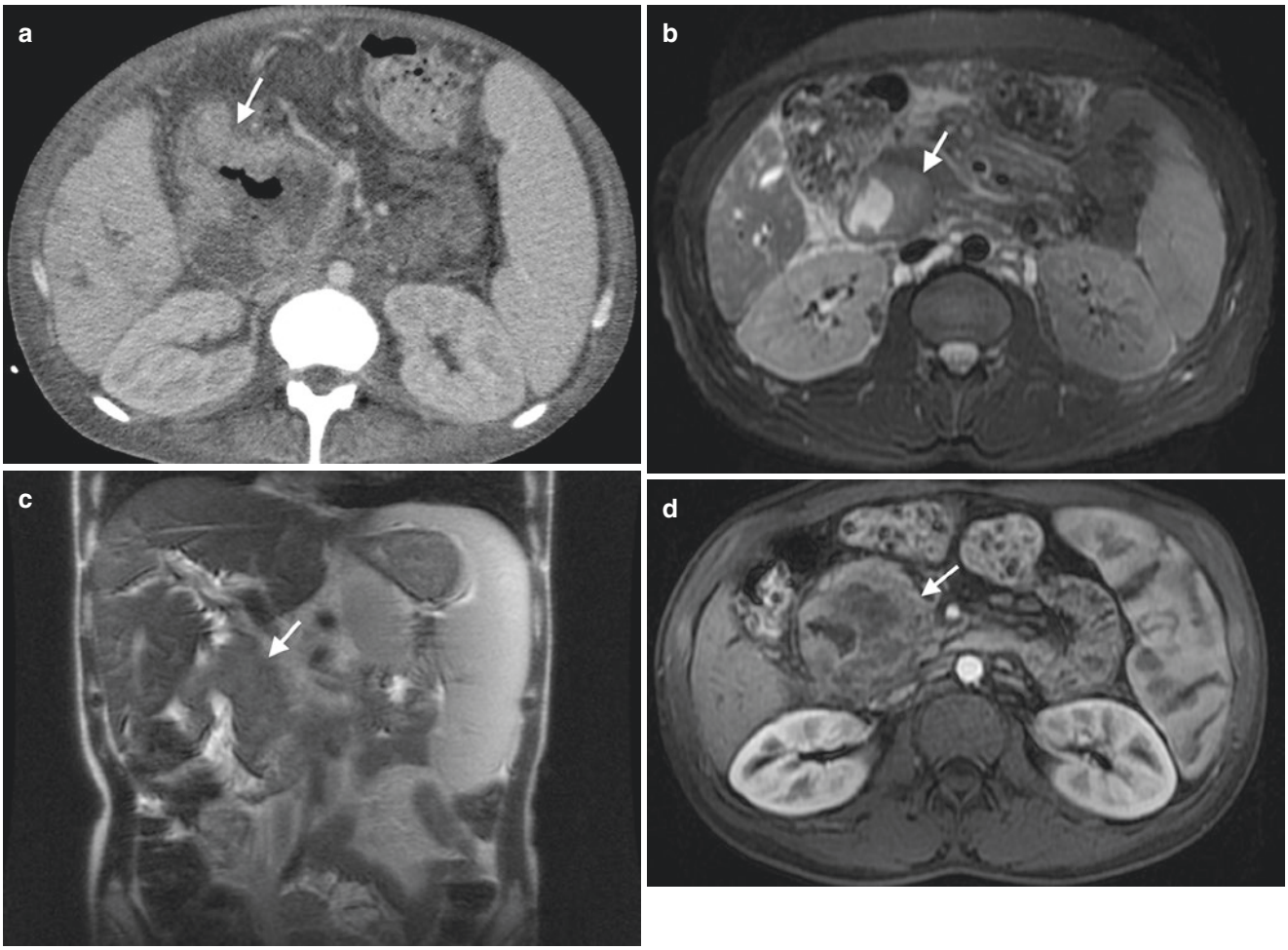
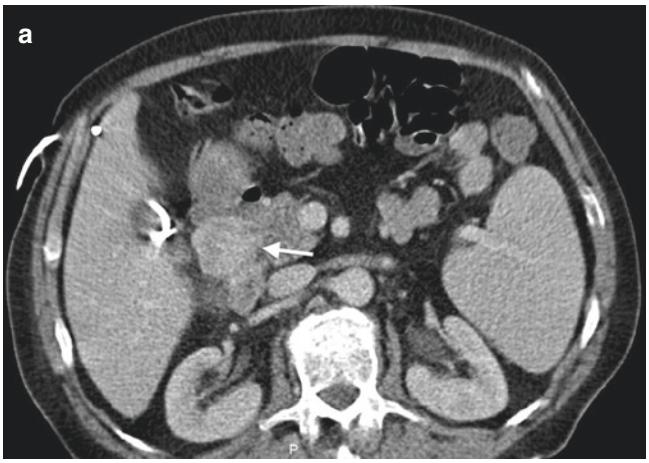


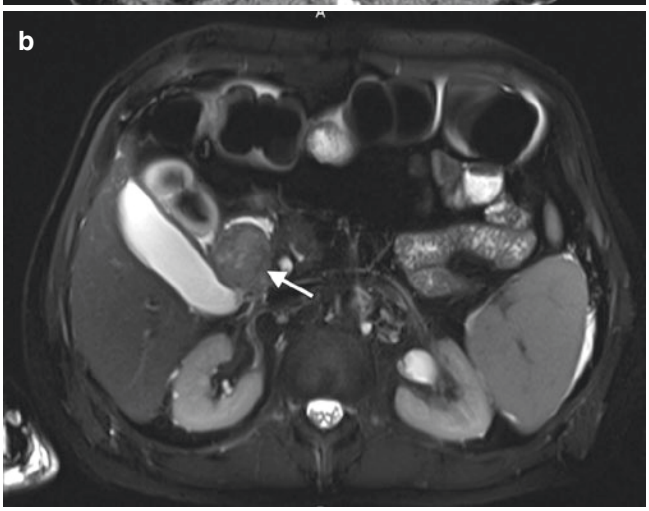
Fig. 25.11 Adenocarcinoma of the duodenum. (**a**) Axial contrast-enhanced CT image demonstrates asymmetric wall thickening (arrow). The same lesion appears as a hypointense lesion (arrows) on (**b**) axial and (**c**) coronal T2-weighted MR images. (**d**) Axial contrast-enhanced MR image reveals heterogeneous contrast enhancement within the mass (arrow)

Gastrointestinal stromal tumors are slow-growing and can affect the small bowel (Fig. 25.12a–c). They mainly develop outside the bowel lumen and, therefore, may present late in the course of the disease. They generally enhance heterogeneously and may contain large necrotic areas. The differential diagnosis of GISTs may be difficult to distinguish from leiomyomas and leiomyosarcomas, as all these tumors tend to present as large solid extraluminally growing masses. Histologically, GISTs may be malignant, potentially malignant, or benign, and differential diagnosis between these different groups may be impossible based on imaging findings alone. However, mass diameter greater than 5 cm, the presence of necrotic component, and irregular external contours with heterogeneous enhancement are imaging features that favor a malignant subtype. Malignant GISTs may be biologically aggressive with distant metastases in addition to locoregional spread [50, 51].

Neuroendocrine tumors (NETs, also called carcinoids) originate from the chromaffin cells from the base of the crypts of Lieberkühn and account for 25% of small bowel tumors. The distal ileum, appendix, and Meckel's diverticulum are the most common locations of NETs [52]. They may present as an enhancing mucosal polyp, parietal nodule, or focal wall thickening [50]. The enhancement is most prominent on arterial phase images. The accompanying extensive fibrosis and sclerosis may give rise to the typical mesenteric retraction and deformation with kinking of the adjacent small bowel loops. The underlying reason for this extensive fibrosis is serotonin release by tumor cells. Small calcified foci within the tumor mass are not unusual, and the distant metastases of NETs are generally hypervascular with intense arterial phase enhancement.

Lymphoma may also affect the small bowel. Primary lymphomas directly arise from the small bowel without any lymph node or other organ involvement, while in secondary lymphomas the epicenter of the disease is extraintestinal with secondary involvement of the bowel segments. The disease may present as diffuse wall thickening or in the form of pol-





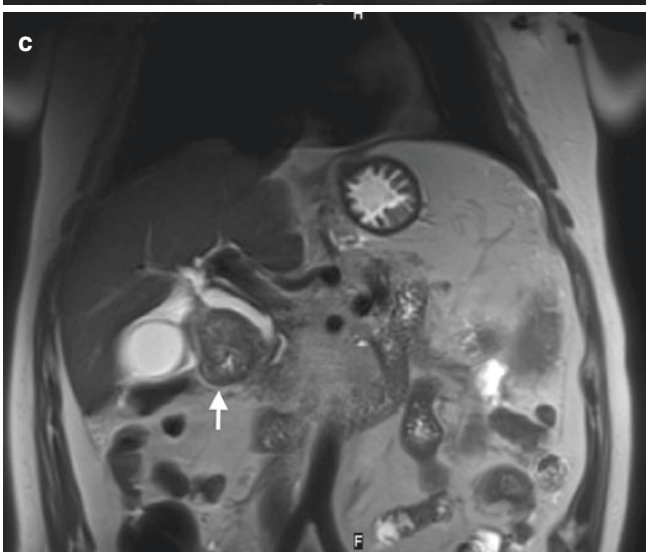
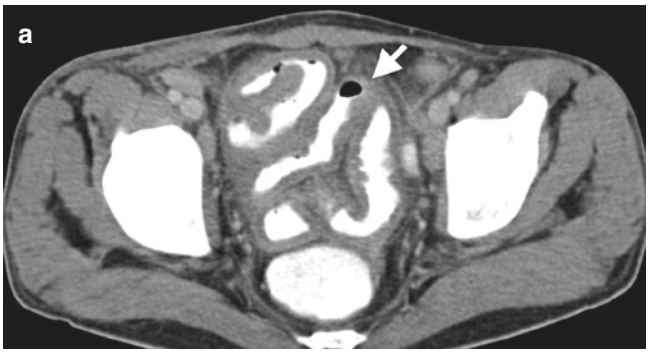


Fig. 25.12 Duodenal gastrointestinal stromal tumor (GIST). (**a**) Axial contrast-enhanced CT of a 74-year-old male demonstrates a well-defined duodenal mass (arrow). (**b**) Axial and (**c**) coronal T2-weighted MR images reveals hypointense mass (arrows) arising from duodenal wall



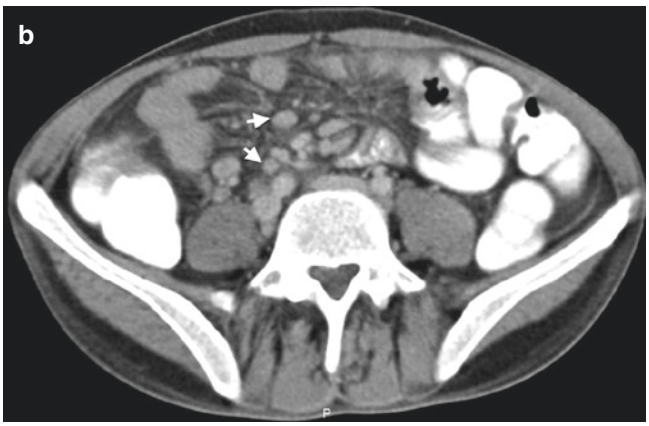


Fig. 25.13 Ileal lymphoma of a 23-year-old male. (**a**) Axial contrast-enhanced CT shows diffuse wall thickening of the ileum due to lymphomatous involvement (arrow). (**b**) Mesenteric lymph nodes (arrows) are also involved

ypoid solid lesions (Fig. 25.13a, b). An important clue for the differential diagnosis for lymphoma is the absence of bowel obstruction despite the disproportionately large tumor mass. In contrast to adenocarcinomas and carcinoids, masses related to lymphoma do not contain prominent fibrotic component, and, therefore, luminal stenosis due to lymphomatous intestinal wall mass is unusual. After contrast injection, the mural mass appears homogenous in contrast to the heterogeneous enhancement nature of other small bowel neoplasms.

Small bowel is a frequent site of distant metastatic disease, and the differential diagnosis of isolated bowel wall metastasis may be difficult to differentiate from primary small bowel carcinomas.

Magnetic Resonance Imaging

MR imaging may also be useful, with its excellent soft tissue resolution, in the evaluation of small bowel neoplasms in select cases. The imaging patterns and findings are not very different from those seen with CT exams. MR may also provide excellent soft tissue contrast regarding the nature of the small bowel tumors [53] (Fig. 25.12a–c).

MR enteroclysis was reported to be a highly sensitive exam for detecting the early superficial changes in the small bowel wall, allowing the diagnosis of the neoplastic process at an earlier stage [54]. Despite its excellent soft tissue contrast, the main drawback of MR enteroclysis is its relatively invasive nature due the requirement of a nasojejunal tube insertion. MR enterography is a noninvasive technique that requires ingestion of a large amount of fluid, which some patients may find difficult to tolerate. The consistency of distension in the jejunal and ileal loops is worse in MR enterography as compared to MR enteroclysis [53].

Positron Emission Tomography-Computed Tomography

PET-CT has a unique ability of combining the anatomic and functional techniques and therefore provides a great opportunity for differential diagnosis. In appropriate clinical settings, the cognizant use of it may have a substantial impact on the clinical decision-making process. Since its introduction, PET-CT has gained wide acceptance and rapidly gained a foothold in the evaluation of bowel disorders. Small bowel neoplasms show increased focal FDG uptake on PET-CT scans. Adenocarcinomas, GISTs, and metastatic deposits in the bowel wall from other sources may all show focal increased uptake on PET-CT, whereas in lymphomas the FDG uptake is mostly on a long bowel segment [55]. The most common primary tumors that tend to metastasize to the bowel segments are thyroid, melanoma, breast, and lung [56].

The detection of the FDG uptake site may guide the endoscopist for higher-yield examination and biopsy and therefore has a potential for a faster diagnosis, especially in the small bowel [55]. It also can play an important role for the initial diagnosis and follow-up of primary small bowel neoplasms.

Somatostatin Receptor-Based Imaging Techniques

Neuroendocrine tumors of the bowel can also be evaluated with functional imaging techniques. These methods mainly depend on the detection of specific cell targets [57]. Somatostatin is an endogenously secreted peptide by the neuroendocrine cells with antiproliferative and antisecretory functions. Somatostatin receptors are expressed with high frequency in well-differentiated NETs [58], and therefore imaging of bowel NETs can be accomplished with targeting somatostatin receptors on NET cells. Usage of gallium-68 (^{68}Ga)-labeled radioligands is a recently developed technique in somatostatin receptor-based imaging. ^{68}Ga is a positron emitter that can bind to somatostatin receptors, and it can be labeled with several somatostatin analogs including ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC, and ^{68}Ga-DOTATATE [58, 59]. Uptake of ^{68}Ga-labeled radioligands can be measured by PET scan, and spatial resolution of ^{68}Ga-PET studies is also improved with fusion of CT images.

^{68}Ga-DOTANOC–PET-CT can be used to detect and localize the primary NETs and their metastases and therefore can be used for several purposes including staging, follow-up, and detecting the recurrent disease. It is also useful for selecting patients for peptide receptor radionuclide therapy (PRRT) [58].

The location and extension of the bowel carcinoids can also be assessed with ^{68}GA-DOTANOC–PET-CT [60]. ^{68}Ga-labeled somatostatin analogs were shown to be more successful for detecting NETs and its metastases as well as the tumor-involved lymph nodes when compared to OctreoScan [61]. Uptake of ^{68}Ga-labeled somatostatin analogs in tumor tissues can be quantitatively assessed by using the maximum standard uptake values (SUV_{max}) in PET-CT studies. This quantitative assessment can be helpful for objective evaluation of treatment response. Sensitivity, specificity, and accuracy of PET-CT studies by using the ^{68}Ga-labeled somatostatin receptor analogs are high for the diagnosis of NETs, and this technique was shown to provide positive clinical impact for the pre-therapy staging [57].

Imaging in Malignant Disease of the Colon and Anorectal Region

General Overview

Colorectal cancers are among the most common malignancies and ranked as the third most common cancer. There are 1.2 million new cases reported with 600,000 deaths per year, ranking as the fourth most common cause of global cancer mortality [62]. It is most commonly seen after the fifth decade, and median age at diagnosis is about 70 years in the developed parts of the world [63].

Stage at the time of diagnosis is crucial for selecting the proper treatment protocol. On CT, colon cancer most frequently presents with asymmetric wall thickening (Figs. 25.14a, b and 25.15a, b). MRI is increasingly being used in the local staging of rectal cancers with high success rates. All cross-sectional anatomic and functional imaging modalities are being used frequently for the detection of distant metastatic disease.

The last decades have witnessed significant improvements in the endoscopic techniques. Currently, endoscopy is the main tool for the diagnosis of rectal cancers, making the use of MRI for primary diagnostic purposes secondary in this regard. However, MRI plays a pivotal role in the local staging of the disease at the time of the diagnosis, as well as the follow-up after neoadjuvant chemoradiotherapy.

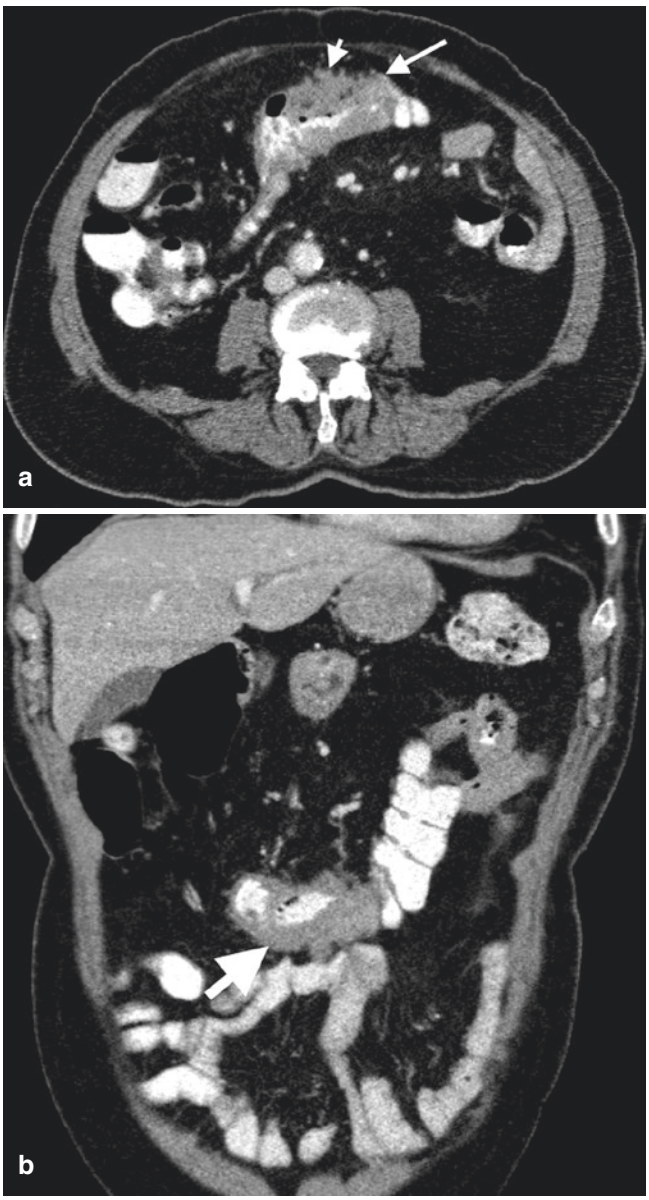


Fig. 25.14 Colon cancer. (**a**) Axial and (**b**) coronal contrast-enhanced CT images demonstrate asymmetric wall thickening (arrows) in the transverse colon and tumor spread into the pericolonic fat (arrowhead)

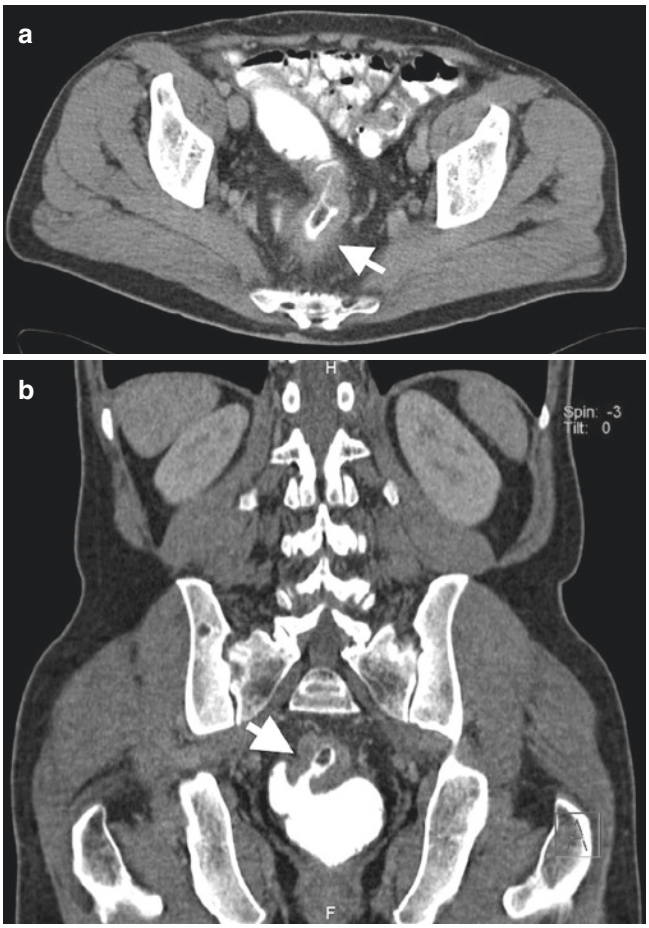


Fig. 25.15 Rectal cancer. (**a**) Axial and (**b**) coronal contrast-enhanced CT images reveal malignant mural thickening (arrows) causing marked luminal narrowing

PET-CT can be used in the diagnosis of colon cancer. Malignant wall thickening appears with avid FDG uptake (Fig. 25.16a–c). Recurrent colon cancers in anastomosis sites can also be detected with PET-CT (Fig. 25.17a–c).

Use of Magnetic Resonance Imaging for Local Staging in Rectal Cancer

Currently, surgery, coupled with stage-appropriate treatment with chemoradiotherapy, is the mainstay of the treatment in rectal cancers. With the widespread acceptance and adoption of the total mesorectal excision (TME), the prevalence of local recurrence has declined from 38% to less than 10% [64]. From a technical standpoint, TME entails en bloc removal of the primary rectal tumor and the mesorectum by means of dissecting along the mesorectal fascial plane or the circumferential resection margin (CRM) [64]. Even with successful TME, the presence of a lymph node involved with tumor spread within 1 mm of the CRM is a significant risk factor for local recurrence [65]. For all the reasons stated earlier, reliable and proper imaging is vital for successful treatment planning (Fig. 25.18a–f).

The timing of the use of radiotherapy in primary rectal cancers is controversial with randomized trials showing low or no benefit in T1 and T2 stage cancers and early favorable-risk T3 stage cancers (less than 5 mm invasion outside muscularis propria). The success of radiotherapy for decreasing local recurrence is more pronounced in advanced stage 3 tumors (more than 5 mm invasion outside muscularis propria) [66].

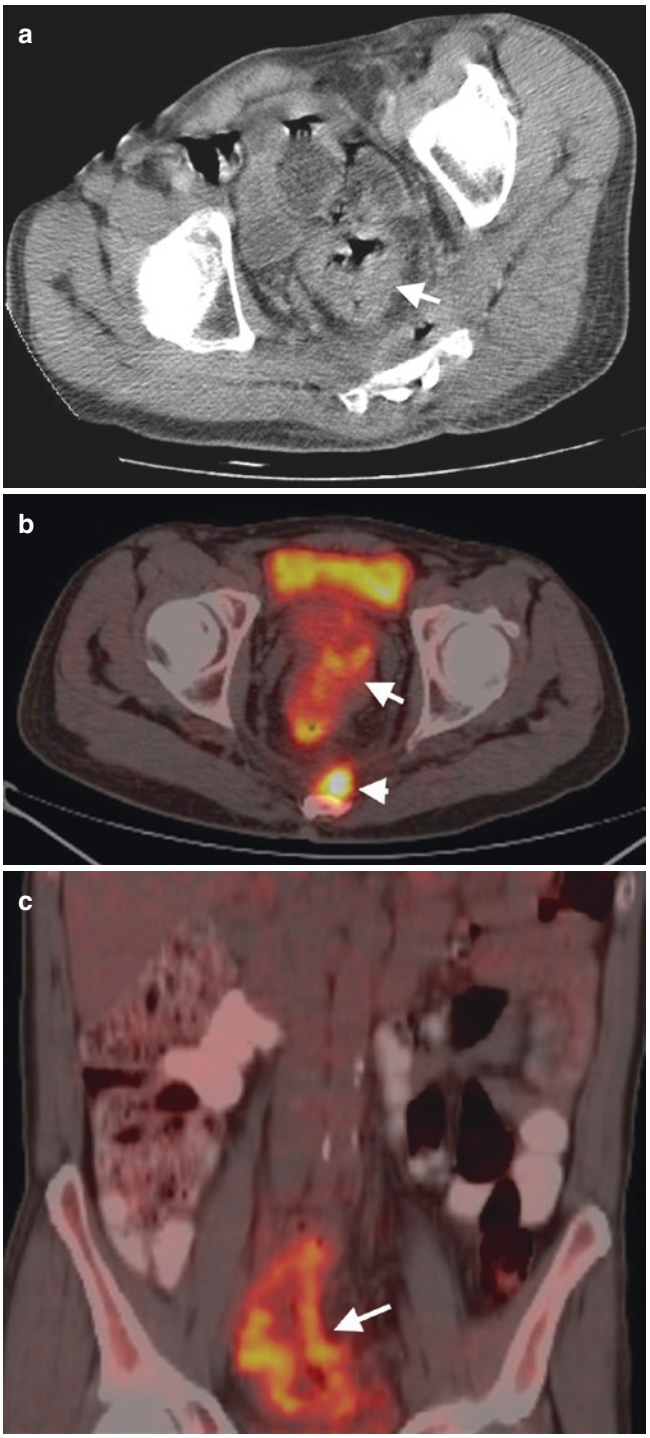


Fig. 25.16 Rectal cancer. (**a**) Axial contrast-enhanced CT image demonstrates malignant mural thickening (arrow). (**b**) Axial and (**c**) coronal PET-CT images reveal avid FDG uptake in rectal cancer (arrows). Axial PET-CT image shows malignant presacral lymph node (arrowhead) with FDG uptake

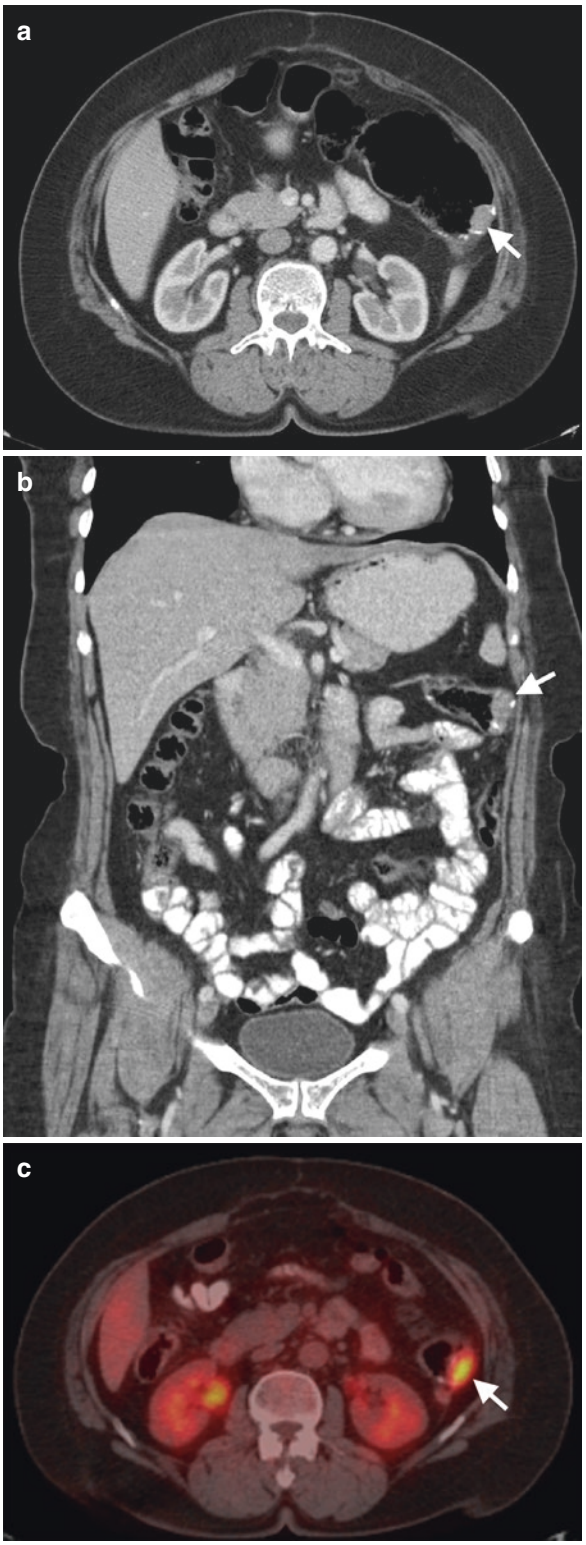


Fig. 25.17 Recurrence of colon cancer. (**a**) Axial and (**b**) coronal CT images reveal nodular wall thickening in the anastomosis site (arrows) that represents recurrence of colon cancer. (**c**) PET-CT image demonstrates FDG uptake in the lesion indicating malignant wall thickening (arrow)

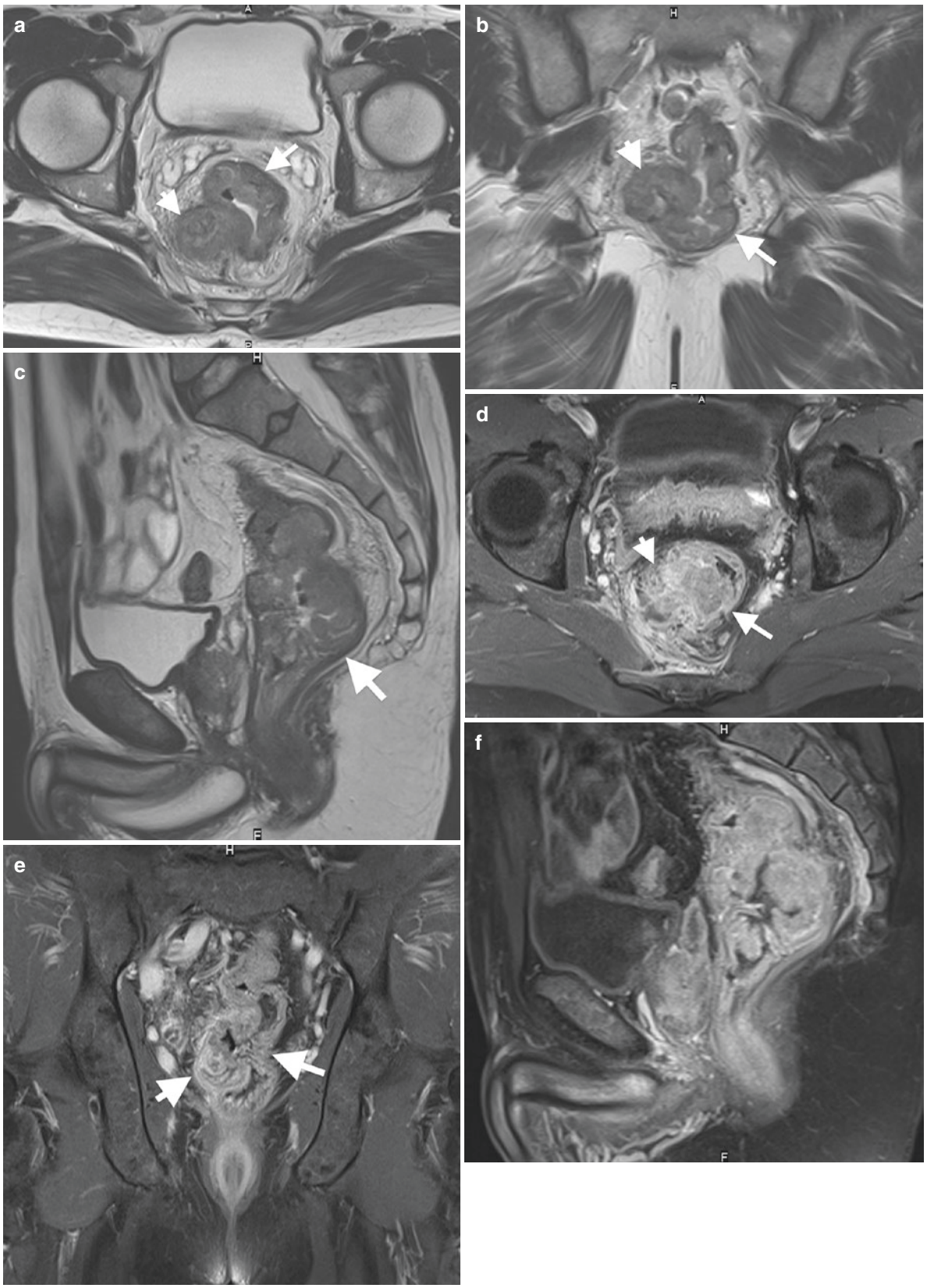


Fig. 25.18 Rectal cancer. (**a**) Axial, (**b**) coronal, and (**c**) sagittal T2-weighted MR images of a 39-year-old female reveal prominent hypointense thickening of the rectal wall (arrows). Perirectal fat tissue involvement is clearly seen (arrowheads). (**d**) Contrast-enhanced axial, (**e**) coronal, and (**f**) sagittal T1-weighted fat-saturated images reveal intense enhancement of the tumor (arrows)

The assessment of the lymph nodes is also crucial in addition to local T staging of the tumor. Mesorectal, superior rectal, retroperitoneal, iliac, inguinal and superior rectal, and inferior mesenteric nodes should all be carefully assessed in terms of involvement from the primary source [67]. In case of malignant lymph node or tumor deposits abutting (i.e., is less than 1 mm from) the mesorectal fascia, this should be included in the report so that the surgeon stays well clear of the tumor at that margin [67]. The detection of the extramesorectal lymph nodes is also important as these lymph nodes may be targeted by adjusting the field for radiation therapy or by widening the surgical excision field. The main limitation of MR imaging in lymph node assessment is its limited sensitivity. Size criterion is most commonly used for nodal tumoral infiltration. The limited success of size criterion is likely due to the fact that 30–50% of metastases in rectal cancer occur in nodes less than 5 mm [67, 68]. There are some other proposed imaging features for the diagnosis of lymph node infiltration such as irregular or spiculated nodal margin and heterogeneous signal intensity. With the introduction of high-resolution MR sequences, these features may help to the correct diagnosis of lymph node infiltration [69].

Extramural vascular invasion (EVI) is defined as the invasion of a vessel located outside the muscularis propria in the primary tumor area. Several studies have showed that the presence of EVI is an important predictor of both local and distant failures [70]. It typically appears as a serpiginous tumor signal extending through the rectal wall into the adjacent vessels [71].

Radiologic Imaging for Colon Cancer Screening

The development of colon cancer is a multistep process and thought to develop from malignant transformation of colonic polyps via adenoma-carcinoma sequence [72]. The estimated interval for this malignant transformation, for a polyp smaller than 1 cm in diameter, is thought to take an average of 10 years, which allows a window of opportunity for early detection and intervention [73]. Currently, there is a wide consensus that mortality from colorectal cancer screening can be reduced via early detection and removal of adenomas before they degenerate into invasive cancers.

The detection rate of the colonic polyps increases dramatically after the age of 50, which is the age at which colorectal cancer screening is recommended to start in average-risk individuals [73, 74]. Fecal occult blood test, endoscopic rectosigmoidoscopy, and colonoscopy are all recommended methods for colorectal cancer screening. However, current guidelines recommend the evaluation of the entire colon either with endoscopic colonoscopy or radiologic imaging tests [74].

Computed Tomography Colonography

Conventional methods of single- or double-contrast barium enema studies for colon cancer screening are now being more commonly replaced by CT colonography (CTC). Advances in CT technology facilitated the use of CTC studies in colorectal cancer screening in the early 1990s. The use of advanced CT techniques allows two-dimensional and three-dimensional evaluation of the colon after proper colonic cleansing.

Commercially available computer-aided detection (CAD) algorithms are also being used more and more frequently in the evaluation of the CTC studies. It may be especially useful for increasing the sensitivity of polyp detection among the less experienced readers of CTC as well as for reducing the inter-reader variability. CAD algorithms are most commonly used as a secondary reader to detect the missed lesions; they also can be used in a confirmatory role in the presence of already detected lesions. With the use of CAD algorithms as a second reader, it was reported that the sensitivity of polyp detection increased by 9–21% with a decreased specificity by 1–4% [75–78].

CTC and endoscopic colonoscopy are comparable when both are used for screening purposes, and both tests resulted in similar rates of detecting advanced cancer; however, more polypectomies were performed in the endoscopic colonoscopy group [79]. Another study reported that in a 5-year follow-up of more than 1000 patients with negative screening, CTC revealed only one interval cancer development, which suggests that CTC may be effectively used as a screening test when performed at 5-year intervals [80].

Patient preparation and lack of patient compliance to routine CTC protocols are the main drawbacks of CTC exams, but several preparation regimens that necessitate minimal or, even, no patient contribution have also been suggested [74].

Another important point to be considered is the cumulative radiation dose related to iterative colorectal cancer screening with CTC. With the advent of new dose-reduction algorithms and iterative reconstruction techniques, the radiation dose with CTC has decreased to levels equivalent to or less than the annual background radiation; the repeat tests with 5-year intervals offer a very favorable benefit-to-risk ratio [74].

Magnetic Resonance Colonography

MR colonography (MRC) has also recently been adopted as a screening tool for colorectal cancers. The introduction of MRC is relatively new compared to CTC. Initially the main limitations of MRC were its poor spatial resolution, exhaustive use of post-processing programs, and residual air bubbles that were easily confused with polyps. However, several advances in the MR technology have now made it possible for the adoption of MRC as a screening tool. MRC is more

commonly utilized in Europe than in the United States. The main underlying reason for this is the wide availability of CTC in the United States compared to more experience with MRC in Europe [74]. With the current state-of-the-art MR technology, an optimal MRC exam can be performed in 20–25 minutes.

As there is no ionizing radiation with MRC, it will not be surprising to see that it will be more commonly used in the future of colorectal cancer screening.

Conclusion

Imaging is widely used in both the diagnosis and follow-up of gastrointestinal cancers. With the advanced imaging techniques (i.e., functional imaging, diffusion-weighted imaging, perfusion studies, etc.), one can easily predict that imaging will be used much more commonly in the future for this purpose. In order to acquire the maximum benefit from an imaging study, it is crucial to know the distinct advantages and limitations of a particular study. An imaging expert should be consulted in complex cases for the selection of the correct imaging study pertinent to the particular patient.

References

1. Pourhoseingholi MA, Vahedi M, Baghestani AR. Burden of gastrointestinal cancer in asia; an overview. Gastroenterol Hepatol Bed Bench. 2015;8(1):19–27.
2. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381(9864):400–12.
3. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349(23):2241–52.
4. Pennathur A, Farkas A, Krasinskas AM, Ferson PF, Gooding WE, Gibson MK, et al. Esophagectomy for t1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. Ann Thorac Surg. 2009;87(4):1048–54; discussion 1054-1045.
5. Lepage C, Rachet B, Jooste V, Faivre J, Coleman MP. Continuing rapid increase in esophageal adenocarcinoma in England and Wales. Am J Gastroenterol. 2008;103(11):2694–9.
6. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst. 2005;97(2):142–6.
7. Fitzgerald RH Jr, Bartles DM, Parker EF. Tracheoesophageal fistulas secondary to carcinoma of the esophagus. J Thorac Cardiovasc Surg. 1981;82(2):194–7.
8. Mandard AM, Chasle J, Marnay J, Villedieu B, Bianco C, Roussel A, et al. Autopsy findings in 111 cases of esophageal cancer. Cancer. 1981;48(2):329–35.
9. Sannohe Y, Hiratsuka R, Doki K. Lymph node metastases in cancer of the thoracic esophagus. Am J Surg. 1981;141(2):216–8.
10. Iyer RB, Silverman PM, Tamm EP, Dunnington JS, DuBrow RA. Diagnosis, staging, and follow-up of esophageal cancer. AJR Am J Roentgenol. 2003;181(3):785–93.
11. Tirumani H, Rosenthal MH, Tirumani SH, Shinagare AB, Krajewski KM, Ramaiya NH. Esophageal carcinoma: current concepts in the role of imaging in staging and management. Can Assoc Radiol J. 2015;66(2):130–9.
12. Halvorsen RA Jr, Thompson WM. Ct of esophageal neoplasms. Radiol Clin N Am. 1989;27(4):667–85.
13. Pongpornsup S, Posri S, Totanarungroj K. Diagnostic accuracy of multidetector computed tomography (mdct) in evaluation for mediastinal invasion of esophageal cancer. J Med Assoc Thail. 2012;95(5):704–11.
14. Kim TJ, Kim HY, Lee KW, Kim MS. Multimodality assessment of esophageal cancer: preoperative staging and monitoring of response to therapy. Radiographics. 2009;29(2):403–21.
15. Munden RF, Macapinlac HA, Erasmus JJ. Esophageal cancer: the role of integrated ct-pet in initial staging and response assessment after preoperative therapy. J Thorac Imaging. 2006;21(2):137–45.
16. van Westreenen HL, Westerterp M, Bossuyt PM, Pruim J, Sloof GW, van Lanschot JJ, et al. Systematic review of the staging performance of 18f-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol. 2004;22(18):3805–12.
17. Karaosmanoglu AD, Blake MA. Applications of pet-ct in patients with esophageal cancer. Diagn Interv Radiol. 2012;18(2):171–82.
18. Levine EA, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, et al. Predictive value of 18-fluoro-deoxy-glucose-positron emission tomography (18f-fdg-pet) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. Ann Surg. 2006;243(4):472–8.
19. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. Pet to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the munich phase ii trial. Lancet Oncol. 2007;8(9):797–805.
20. Hallinan JT, Venkatesh SK. Gastric carcinoma: imaging diagnosis, staging and assessment of treatment response. Cancer Imaging. 2013;13:212–27.
21. Arnold M, Moore SP, Hassler S, Ellison-Loschmann L, Forman D, Bray F. The burden of stomach cancer in indigenous populations: a systematic review and global assessment. Gut. 2014;63(1):64–71.
22. Parkin DM, Bray FI. Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer. 2001;37(Suppl 8):S4–66.
23. Davies J, Chalmers AG, Sue-Ling HM, May J, Miller GV, Martin IG, et al. Spiral computed tomography and operative staging of gastric carcinoma: a comparison with histopathological staging. Gut. 1997;41(3):314–9.
24. Sheybani A, Menias CO, Luna A, Fowler KJ, Hara AK, Silva AC, et al. Mri of the stomach: a pictorial review with a focus on oncological applications and gastric motility. Abdom Imaging. 2015;40(4):907–30.
25. Malibari N, Hickeson M, Lisbona R. Pet/computed tomography in the diagnosis and staging of gastric cancers. PET Clin. 2015;10(3):311–26.
26. Stahl A, Ott K, Weber WA, Becker K, Link T, Siewert JR, et al. Fdg pet imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. Eur J Nucl Med Mol Imaging. 2003;30(2):288–95.
27. Chen J, Cheong JH, Yun MJ, Kim J, Lim JS, Hyung WJ, et al. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. Cancer. 2005;103(11):2383–90.
28. Yeung HW, Macapinlac H, Karpeh M, Finn RD, Larson SM. Accuracy of fdg-pet in gastric cancer. Preliminary experience. Clin Positron Imaging. 1998;1(4):213–21.
29. Alakus H, Batur M, Schmidt M, Drebber U, Baldus SE, Vallbohmer D, et al. Variable 18f-fluorodeoxyglucose uptake in gastric cancer is associated with different levels of glut-1 expression. Nucl Med Commun. 2010;31(6):532–8.
30. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. Fdg pet evaluation of mucinous neoplasms: correlation of fdg uptake with histopathologic features. AJR Am J Roentgenol. 2000;174(4):1005–8.

31. Landry J, Tepper JE, Wood WC, Moulton EO, Koerner F, Sullinger J. Patterns of failure following curative resection of gastric carcinoma. Int J Radiat Oncol Biol Phys. 1990;19(6):1357–62.
32. Lehnert T, Rudek B, Buhl K, Golling M. Surgical therapy for locoregional recurrence and distant metastasis of gastric cancer. Eur J Surg Oncol. 2002;28(4):455–61.
33. Roukos DH. Extended (d2) lymph node dissection for gastric cancer: do patients benefit? Ann Surg Oncol. 2000;7(4):253–5.
34. Shreve PD, Anzai Y, Wahl RL. Pitfalls in oncologic diagnosis with fdg pet imaging: physiologic and benign variants. Radiographics. 1999;19(1):61–77; quiz 150-151.
35. Levy AD, Shaw JC, Sobin LH. Secondary tumors and tumorlike lesions of the peritoneal cavity: imaging features with pathologic correlation. Radiographics. 2009;29(2):347–73.
36. Low RN. Mr imaging of the peritoneal spread of malignancy. Abdom Imaging. 2007;32(3):267–83.
37. Vicens RA, Patnana M, Le O, Bhosale PR, Sagebiel TL, Menias CO, et al. Multimodality imaging of common and uncommon peritoneal diseases: a review for radiologists. Abdom Imaging. 2015;40(2):436–56.
38. Park CM, Kim SH, Kim SH, Moon MH, Kim KW, Choi HJ. Recurrent ovarian malignancy: patterns and spectrum of imaging findings. Abdom Imaging. 2003;28(3):404–15.
39. Hamrick-Turner JE, Chiechi MV, Abbitt PL, Ros PR. Neoplastic and inflammatory processes of the peritoneum, omentum, and mesentery: diagnosis with ct. Radiographics. 1992;12(6):1051–68.
40. Jacquet P, Jelinek JS, Steves MA, Sugarbaker PH. Evaluation of computed tomography in patients with peritoneal carcinomatosis. Cancer. 1993;72(5):1631–6.
41. Walkey MM, Friedman AC, Sohotra P, Radecki PD. Ct manifestations of peritoneal carcinomatosis. AJR Am J Roentgenol. 1988;150(5):1035–41.
42. Whitley NO, Bohlman ME, Baker LP. Ct patterns of mesenteric disease. J Comput Assist Tomogr. 1982;6(3):490–6.
43. De Gaetano AM, Calcagni ML, Rufini V, Valenza V, Giordano A, Bonomo L. Imaging of peritoneal carcinomatosis with fdg pet-ct: diagnostic patterns, case examples and pitfalls. Abdom Imaging. 2009;34(3):391–402.
44. Turlakow A, Yeung HW, Salmon AS, Macapinlac HA, Larson SM. Peritoneal carcinomatosis: role of (18)f-fdg pet. J Nucl Med. 2003;44(9):1407–12.
45. Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer. 2004;101(3):518–26.
46. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249(1):63–71.
47. Haselkorn T, Whittemore AS, Lilienfeld DE. Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. Cancer Causes Control. 2005;16(7):781–7.
48. Reynolds I, Healy P, McNamara DA. Malignant tumours of the small intestine. Surgeon. 2014;12(5):263–70.
49. Kadakia SC, Parker A, Canales L. Metastatic tumors to the upper gastrointestinal tract: endoscopic experience. Am J Gastroenterol. 1992;87(10):1418–23.
50. Algin O, Evrimler S, Arslan H. Advances in radiologic evaluation of small bowel diseases. J Comput Assist Tomogr. 2013;37(6):862–71.
51. Horton KM, Juluru K, Montogomery E, Fishman EK. Computed tomography imaging of gastrointestinal stromal tumors with pathology correlation. J Comput Assist Tomogr. 2004;28(6):811–7.
52. Druce M, Rockall A, Grossman AB. Fibrosis and carcinoid syndrome: from causation to future therapy. Nat Rev Endocrinol. 2009;5(5):276–83.
53. Masselli G, Gualdi G. Mr imaging of the small bowel. Radiology. 2012;264(2):333–48.
54. Masselli G, Casciani E, Polettini E, Gualdi G. Comparison of mr enteroclysis with mr enterography and conventional enteroclysis in patients with crohn's disease. Eur Radiol. 2008;18(3):438–47.
55. Das CJ, Manchanda S, Panda A, Sharma A, Gupta AK. Recent advances in imaging of small and large bowel. PET Clin. 2016;11(1):21–37.
56. Anzidei M, Napoli A, Zini C, Kirchin MA, Catalano C, Passariello R. Malignant tumours of the small intestine: a review of histopathology, multidetector ct and mri aspects. Br J Radiol. 2011;84(1004):677–90.
57. Tan EH, Tan CH. Imaging of gastroenteropancreatic neuroendocrine tumors. World J Clin Oncol. 2011;2(1):28–43.
58. Maxwell JE, Howe JR. Imaging in neuroendocrine tumors: an update for the clinician. Int J Endocr Oncol. 2015;2(2):159–68.
59. Sundin A. Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol [Review]. 2012;26(6):803–18.
60. Jain TK, Karunanithi S, Dhull VS, Roy SG, Kumar R. Carcinoma of unknown primary of neuroendocrine origin: accurate detection of primary with (68)ga-labelled [1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid]-1-nai3-octreotide positron emission tomography/computed tomography enterography. Indian J Nucl Med. 2014;29(2):122–3.
61. Krausz Y, Freedman N, Rubinstein R, Lavie E, Orevi M, Tshori S, et al. 68ga-dota-noc pet/ct imaging of neuroendocrine tumors: comparison with (1)(1)(1)in-dtpa-octreotide (octreoscan(r)). Mol Imaging Biol [Clinical Trial Comparative Study]. 2011;13(3):583–93.
62. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383(9927):1490–502.
63. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62(4):220–41.
64. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg. 1998;133(8):894–9.
65. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet. 1986;2(8514):996–9.
66. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638–46.
67. Kaur H, Choi H, You YN, Rauch GM, Jensen CT, Hou P, et al. Mr imaging for preoperative evaluation of primary rectal cancer: practical considerations. Radiographics. 2012;32(2):389–409.
68. Dworak O. Number and size of lymph nodes and node metastases in rectal carcinomas. Surg Endosc. 1989;3(2):96–9.
69. Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution mr imaging with histopathologic comparison. Radiology. 2003;227(2):371–7.
70. Horn A, Dahl O, Morild I. The role of venous and neural invasion on survival in rectal adenocarcinoma. Dis Colon Rectum. 1990;33(7):598–601.
71. Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. Br J Surg. 2003;90(3):355–64.
72. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. Cancer. 1975;36(6):2251–70.

73. Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112(2):594–642.
74. Levine MS, Yee J. History, evolution, and current status of radiologic imaging tests for colorectal cancer screening. Radiology. 2014;273(2 Suppl):S160–80.
75. Baker ME, Bogoni L, Obuchowski NA, Dass C, Kendzierski RM, Remer EM, et al. Computer-aided detection of colorectal polyps: can it improve sensitivity of less-experienced readers? Preliminary findings. Radiology. 2007;245(1):140–9.
76. Dachman AH, Obuchowski NA, Hoffmeister JW, Hinshaw JL, Frew MI, Winter TC, et al. Effect of computer-aided detection for ct colonography in a multireader, multicase trial. Radiology. 2010;256(3):827–35.
77. Petrick N, Haider M, Summers RM, Yeshwant SC, Brown L, Iuliano EM, et al. Ct colonography with computer-aided detection as a second reader: observer performance study. Radiology. 2008;246(1):148–56.
78. Regge D, Della Monica P, Galatola G, Laudi C, Zambon A, Correale L, et al. Efficacy of computer-aided detection as a second reader for 6-9-mm lesions at ct colonography: Multicenter prospective trial. Radiology. 2013;266(1):168–76.
79. Kim DH, Pickhardt PJ, Taylor AJ, Leung WK, Winter TC, Hinshaw JL, et al. Ct colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med. 2007;357(14):1403–12.
80. Kim DH, Pooler BD, Weiss JM, Pickhardt PJ. Five year colorectal cancer outcomes in a large negative ct colonography screening cohort. Eur Radiol. 2012;22(7):1488–94.

Immunological Treatment in Gastrointestinal Cancers

26

Héctor Randhall Callata-Carhuapoma
and Jesús García-Foncillas López

Introduction

Colorectal cancer is the third most common malignancy in men and the second in women, with 746,000 and 614,000 estimated new cases in 2012, respectively; it constitutes the fourth cause of cancer death worldwide [1]. For example, colorectal cancer incidence is steadily increasing in Spain with about 32,000 estimated new cases reported in 2012. It is estimated there will be about 246,000 new cases in 2020 in Spain [2].

The relative survival rate for colorectal cancer is 65% at 5 years after diagnosis and 58% at 10 years. Only 40% of patients are diagnosed with localized-stage colorectal cancer in the United States, for which the 5-year survival rate is 90% [3]. Survival declines to 70% for patients with regional lymph node involvement and to 13% for patients with distant metastases [3]. Although surgery is a curative treatment, recurrence is frequent, with a rate between 0% and 13% for stage 1, 11% and 61% for stage 2, and 32% and 88% for stage 3 [4]. Patients with high risk of recurrence receive chemotherapy, and patients with metastatic disease are treated with palliative chemotherapy and targeted therapies. However, despite recent progress in treatment strategies, the prognosis of advanced colorectal cancer remains poor [5].

Recent advances in the understanding of the genetic mechanisms of carcinogenesis of colorectal cancer [6] and the immune tumor microenvironment have allowed the development of new strategies for investigation with immune-based biomarkers and the development of new therapeutic agents that target immune pathways [7].

Antitumor Immune Mechanisms in Colorectal Cancer

Immune Surveillance

The role of the immune system against cancer was speculated by Ehrlich in 1909, who proposed that the immune system could stop the growth of malignant cells. About 50 years later, Burnet and Thomas elaborated on the concept of immunosurveillance as the competence of the immune system to develop a reaction against tumor cell-specific neoantigens that suppress the tumor growth before clinical expression. However, this concept of immunosurveillance was forgotten until the past decade [8].

The first observations about immunosurveillance were recorded upon seeing the cohorts of patients with human immunodeficiency virus (HIV) infection, who had higher incidences of cancer compared to normal, uninfected patients [9]. Then, this concept of immunosurveillance was demonstrated in 2001 in animal models, when it was observed that immunocompetent mice did not develop any neoplasia, while RAG2-/- mice, deficient in lymphocytes T and B, developed malignant neoplasias more frequently [10].

Immunoediting

Complementary to the concept of immune surveillance, the concept of immunoediting was proposed in 2002, which refers to the interaction between cancer and the immune system, allowing cancer cells to escape from the immune surveillance [11].

Immune Escape

Finally, after complex interaction between tumor cells and the immune system, the selected pressure exerted on tumor cells allows the emergence of resistant clones. This process

H. R. Callata-Carhuapoma · J. García-Foncillas López (✉)
Department of Oncology, University Hospital Fundacion Jimenez Diaz – Autonomous University of Madrid, Madrid, Spain
e-mail: jesus.garciafoncillas@oncohealth.eu

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_26

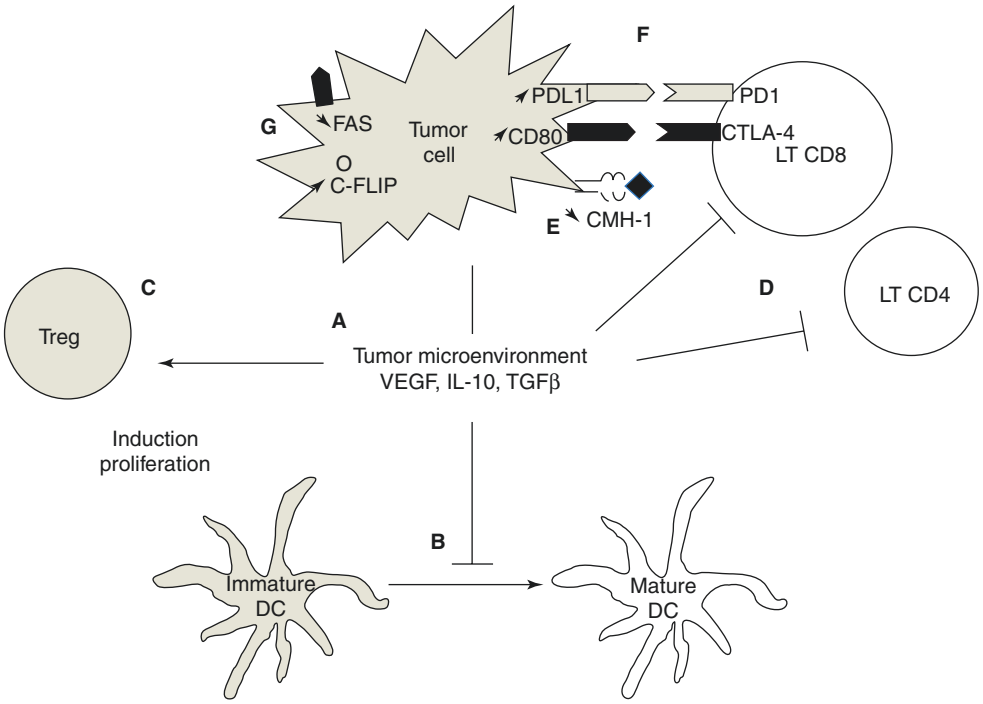


Fig. 26.1 Main mechanisms of tumor immune escape. A: Malignant cells secrete proinflammatory molecules (VEGF, IL-10, TGF-β). B: These molecules block the maturation of dendritic cells. C: Also promote differentiation of Treg. D: Blocks the differentiation of T CD4+ and CD8+ cells. E: Malignant cells downregulate expression of CMH-1. F: Malignant cells promote expression of PD-L1 and CD80 that produces depletion of lymphocytes. G: Finally, malignant cells can promote the expression of antiapoptotic molecules such as C-FLIP and inhibit proapoptotic molecules such as FAS. (Modified from Pernot et al. [8] with permission of Prof. Julien Taiev. All rights reserved)

occurs in 3 phases: (1) the immune surveillance period, with the elimination of the tumor cells; (2) the latency period, in which there is a state of equilibrium; and (3) the phase of escape, or immunoescape, in which appears tumor progression and clinical expression of malignant disease [11, 12]. These complex interactions are summarized in Fig. 26.1 [8].

Innate Immunity

Innate immunity is the first line of defense of the immune system, with specialized cells that recognize tumor-specific antigens on the surface of malignant cells the same way as the recognition of non-self-pathogens.

Natural Killer (NK)

Natural killer (NK) cells express 2 types of receptors: activating and inhibitory receptors. The activator receptors (e.g., NKG2D, NK receptor group 2, member D) can bind different activating ligands overexpressed on tumor cells, while killer inhibitory receptors (e.g., KIR, killer-Ig-like receptor) recognize major histocompatibility complex (MHC) class 1 molecules so that NK cells can be activated by the low expression of MHC class 1 molecules reported in tumor cells [13, 14].

In addition, NK cells have a cytotoxic effect on tumor cells mediated by other mechanisms such as antibody-dependent cell-mediated cytotoxicity (dendritic cells) and secretion of cytokines, as IFN-γ(gamma), as well as the release of cytotoxic granules containing perforin and granzyme B [12, 15].

There are reports that describe the association between extensive intratumoral infiltration of NK cells and better prognosis in colorectal cancer [16].

Natural Killer T (NKT)

Natural killer T (NKT) cells express characteristics of both type of cells, NK and T cells. These cells recognize glycolipid antigens such as galactosylceramide presented by CD1d, an MHC class 1-like molecule that binds self and foreign lipids.

The activation of NKT cells produces secretion of abundant proinflammatory cytokines—interleukin 2 (IL-2), interferon gamma (IFN-γ[gamma]), tumor necrosis factor-alpha (TNF-α), and interleukin 4 (IL-4)—and effector molecules involved in cell death (perforin, FAS ligand, TNF-related apoptosis-inducing ligand [TRAIL]). In the same way as NK cells, an increased tumor infiltration of NKT cells has been associated with better prognosis in colorectal cancer [17].

Macrophages

Tumor-infiltrating macrophages (TIM) can be divided into 2 groups: (1) M1 TIM produces proinflammatory molecules (IL-6, IL-12, IL-23, and TNF-α[alpha]) and promotes the adaptive immunity via increased expression of MHC and costimulatory molecules. (2) Conversely, M2 TIM produces immunosuppressive cytokines (IL-10, transforming growth factor-beta [TGF-β], and prostaglandin E2) and promotes angiogenesis through the production of vascular endothelial growth factor (VEGF), promoting tumor progression.

In several neoplasias, tumor infiltration by macrophages has been associated with poor prognosis [18], while in colorectal cancer, it seems to be associated with better prognosis [19]; however, there are reports that describe the opposite [20].

Adaptive Immunity

Adaptive immunity is responsible for a long-term immune response against tumor cells, including immune memory related to a prior immune challenge. This begins when the antigen-presenting cells, mainly dendritic cells, capture, process, and present tumor antigens to CD4 T cells through MHC class 2 or to CD8 T cells through MHC class 1 [8].

Activation of T cells needs 3 signals: (1) recognition of the specific antigen presented by the antigen-presenting cells, (2) activation of costimulatory molecules (CD80/CD28, CD40/CD40L), and (3) secretion of cytokines (IL-1, IL-2, IL-6, IL-12, IFN-γ[gamma]) [21].

CD8 T cells can recognize and lyse the malignant cells, while CD4 T cells modulate the immune response. Two different functions can be identified: (1) The activity of T cell helper (Th) 1 cells allows secretion of antitumor cytokines, as IL-2 and IFN-γ(gamma), (2) while activity of Th2 cells promotes the tumor growth [12].

A subset of these cells, Th17, produces IL-17A, IL-17F, IL-21, IL-22, IFN-γ(gamma), and GM-CSF. The Th17 type of T cell subset has a controversial role in immunity, having been reported to increase or decrease tumor growth depending on the tumor type or the therapeutic strategy investigated [22, 23]. Recently it was reported there is an association between Lnc-SGK1 (non-coding RNA of serum and glucocorticoid-inducible kinase 1), leading to Th17 and Th2 differentiation, and *Helicobacter pylori* infection with poor prognosis in gastric cancer [24].

Finally, another subset of $CD4^+$ T cells is the regulatory T cells (Tregs), characterized by expression of CD4, CD25 and FOXP3, which have a regulatory function promoting the maintenance of immune self-tolerance and suppressing the immune activity against self-antigens [25]. Some tumor antigens can promote intratumoral proliferation of Tregs favoring cancer-induced immunosuppression. Perhaps therapeutic strategies targeting Tregs could have important favorable outcomes in treatment of cancer patients [21].

Immunotherapy Strategies in Colorectal Cancer

Peptide, protein, whole tumor cell, and dendritic cell vaccines; cytokines; adaptive cell therapy; and monoclonal antibodies are the main immunotherapy strategies for colorectal cancer that have been clinically evaluated [26] (Table 26.1 and Fig. 26.2).

Vaccination

Whole Tumor Vaccines

Whole tumor vaccines are made with tumor tissue that has been lysed or irradiated, mixed with immune adjuvant such as alum, and then reinjected into the patient [27]. These were the earliest of the strategies of vaccination because the material was easily available and contained all of the known and unknown tumor-associated antigens that needed to be eliminated. Thus, while there are no responses against a specific antigen, probably a more diverse immune response could avoid the possibility of tumor immune escape from a more specific vaccine. However, immune response generated by the whole tumor vaccine is poor because the small amounts of the antigens in the whole tumor are specific to those kinds of malignant cells [28, 29].

There are three phase 3 trials with these earliest types of vaccine. In 1993, Hoover et al. did not find a benefit for 80 colorectal cancer patients, stages II and III, with autologous tumor cell-bacillus Calmette-Guerin (BCG) vaccine in the adjuvant setting [30]. In 2000, Harris et al. performed a trial with 412 patients to evaluate autologous tumor cell-BCG and did not find differences between the experimental and control arms [31]. Finally, Vermorken et al. repeated the same protocol and found an improvement in the recurrence-free period (61% risk reduction for recurrences, $p = 0.011$) and recurrence-free survival (42% risk reduction for recurrence or death, $p = 0.032$), and there was a trend toward improved overall survival (OS) [32]. Of note, in all of these trials, the control group was assigned to observation, and they did not receive any adjuvant therapy.

Peptide Vaccines

Because of the limited efficacy of whole tumor vaccines, which develop a poor immune response, new strategies were tried to optimize specific immune response against tumor cells. The therapy with peptide vaccines is based on the identification of a specific tumor antigen that can be recognized by T or B cells. Peptide-based vaccines are whole proteins or fragments of proteins generated from tumor-specific antigens that are administered in conjunction with an adjuvant vaccine molecule (Tables 26.2 and 26.3) [33].

In colorectal cancer, multiple tumor-associated antigens have been identified and used for vaccination, antigens such as β(beta)-human chorionic gonadotropin (β[beta]-HCG) [34], carcinoembryonic antigen (CEA) [35, 36], squamous cell carcinoma antigen recognized by T cells 3 (SART 3) [37], p53 [38], mucin 1 [39], and survivin-2B [40].

The majority of the phase 1 and 2 trials with peptide vaccines did not show clinical benefit. CEA is the most common antigen targeted in clinical trials with this strategy. A phase 2 trial in 56 patients after curative liver metastases resection did not show improvement in 2-year overall survival with the use of anti-idiotype monoclonal antibody vaccines to the tumor-

Table 26.1 Phase 3 trials with various immunotherapy strategies

Immunotherapy strategy	Authors	Journal	Year	Patients (N)	Treatment arms	Follow-up (median)	Results
Vaccine (whole tumor)	Hoover et al. [30]	Journal of Clinical Oncology	1993	80	Autologous tumor cell-BCG after curative surgery of CRC stage II or III vs. surgery alone	93 months (colon cancer patients) and 58 months (rectal cancer patients)	Improved OS and DFS in colon cancer patients, but no benefits were seen in rectal cancer patients
Vaccine (whole tumor)	Vermorken et al. [32]	The Lancet	1999	254	Autologous tumor cell-BCG vaccine after curative surgery of CRC stage II or III vs. surgery alone	5.3 years	Improved recurrence-free survival and trend to improved OS in stage II CRC patients. No benefit in stage III CRC patients
Vaccine (whole tumor)	Harris et al. [31]	Journal of Clinical Oncology	2000	412	Irradiated autologous tumor cell-BCG vaccine after curative surgery of CRC stage II or III vs. surgery alone	7.6 years	Negative study. There was association between magnitudes of delayed cutaneous hypersensitivity with better prognosis
Vaccine (whole tumor)	Schulze et al. [41]	Cancer Immunology Immunotherapy	2009	50	Irradiated NDV-infected autologous tumor cell vaccine after curative resection of liver metastases vs. surgery alone	116 months (experimental arm) and 112 months (control group)	No differences in OS, DFS, and metastases-free survival. However in colon cancer patients, vaccine group has better OS and metastases-free survival
Monoclonal antibody	Fields et al. [106]	Journal of Clinical Oncology	2009	1839	Edrecolomab +5-FU-based chemotherapy after curative surgery of CRC stage III vs. 5-FU-based chemotherapy alone	5 years	Negative study. No differences between both arms
Cytokine treatment	Correale et al. [46]	Journal of Immunotherapy	2014	120	FOLFOX-4 vs. GOLFIG (gemcitabine + oxaliplatin +5-fluoruracil + levofolinate + GM-CSF sc + aldesleukin sc.) in chemotherapy-naïve metastatic CRC patients	43.83 months	Improved PFS and ORR and trend to longer OS in GOLFIG arm

CRC colorectal cancer

associated antigens CEA [36]. In a phase 2 trial of vaccination with β(beta)-HCG peptide in 77 colorectal cancer patients, production of antibodies was induced in 56 of them; also this antibody induction was not associated with longer overall survival [34]. In a trial with SART3 peptide vaccine, antibodies were detected in patients; however, immune response was limited to the patients expressing HLA-A24 [37].

Vaccine trials were made both in advanced disease but also in adjuvant setting. OncoVAX and Newcastle virus-related vaccine (NDV) were developed for the same hypothesis. In a meta-analysis, recurrence-free interval was better in the OncoVAX arm (25% ± 13, $p = 0.05$), and this effect was especially shown for the adjuvant setting [41].

In a phase 3 study of metastasectomized advanced colorectal cancer patients, there were no overall survival or progression-free survival (PFS) benefits; however, in subgroup analysis of patients with colonic tumors, there was a difference in OS and PFS rates (OS HR 3.3, $p = 0.042$; PFS HR 2.7, $p = 0.047$). In spite of this, patients with rectal cancer did not receive any benefit [31].

Phase 1 NCT02600949 trial, a pilot study for applicability and safety in pancreatic and colorectal cancers, continues to recruit patients.

Adoptive Cell Transfer Therapy (ACT)

Adoptive cell transfer therapy (ACT) extracts autologous T cells from tumoral cells of the patient, then these cells are activated with cytokines and grown in vitro, after which this preparation is transferred back into the patient (Table 26.4) [33]. Adoptive cell transfer with T cells from sentinel nodes of 16 colorectal cancer patients with advanced disease has been evaluated; the tolerance was excellent, without adverse effects, and has led to a complete response in 4 of 9 patients [42]. Likewise, there was a report of an improvement in median overall survival using ACT with T cells of sentinel nodes of patients who underwent radical ($n = 46$) or palliative ($n = 25$) surgery of colorectal cancer, without any adverse effect reported in the overall population [43]. However, in a phase 1 trial performed

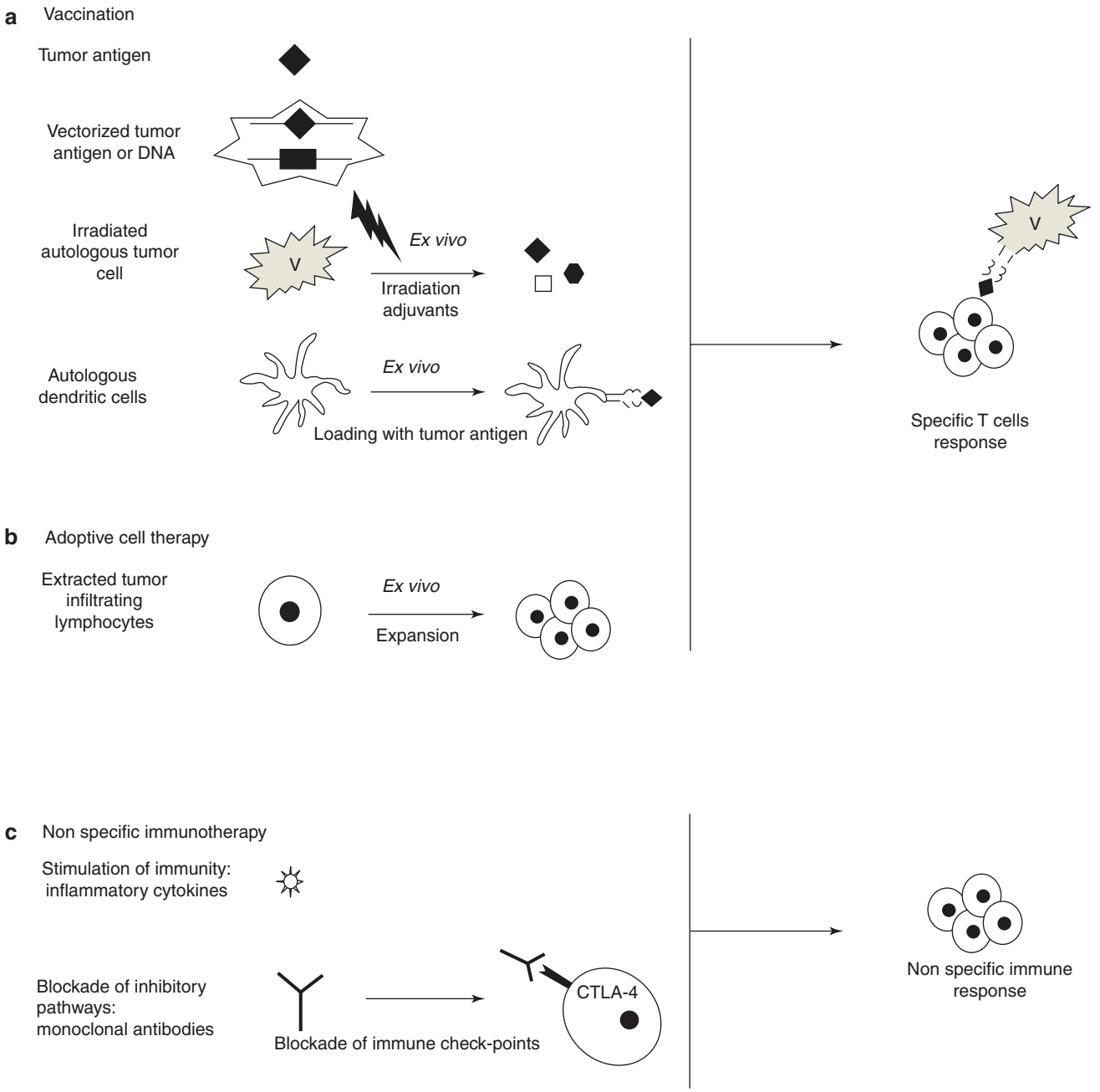


Fig. 26.2 Immunotherapy strategies: A: Vaccination produces an induction of specific response against tumor antigens B: Adoptive cell therapy consists in ex vivo expansion of immune cells of the host. C: Non-specific stimulation of immune system can be reached with administration of proinflammatory cytokines or monoclonal antibodies that blockade inhibitory pathways. (Modified from Pernot et al. [8] with permission of Prof. Julien Taiev. All rights reserved)

by Parkhurst et al., human T cells were modified to express a high-avidity CEA-specific murine T cell receptor. Three metastatic colorectal cancer patients were treated with these cells, and all of them experienced decreased serum CEA levels, and one of them reached an objective response, but all patients developed a severe transient inflammatory colitis, which represented a dose-limiting toxicity [44].

Cytokine Treatment

This non-specific immunotherapy strategy consists of stimulation of the immune system with administration of cytokines such as interferon, interleukins, or granulocyte macrophage colony-stimulating factor (GM-CSF) (Table 26.5) [33].

Table 26.2 Immunotherapy vaccine studies on colorectal cancers

NCT number	Setting	Trial phase	Vaccines	Number of patients	Primary endpoint
NCT02448173	Stage II	III	OncoVAX + surgery vs. surgery	550	Disease-free survival
NCT01890213	Stage III	I	AVX701	12	Adverse events
NCT02718430	mCRC with CLM	I	VXM01	24	Safety and tolerability
NCT01741038	mCRC	II-III	AlloStim® + cryoablation vs. AlloStim + physician's choice	450	Overall survival
NCT02615574	Refractory mCRC	II	áDCI vaccine + CKM	44	Overall survival

Modified from Procaccio et al. [33]. https://creativecommons.org/licenses/by/4.0/
mCRC metastatic colorectal cancer

Table 26.3 Adjuvant therapy studies on colorectal cancers

NCT number	Setting	Trial phase	Adjuvant therapy	Number of patients	Primary endpoint
NCT01545141	Resectable CRC	I–II	Surgery vs. chemokine modulatory regimen (a combination of interferon, celecoxib, and rintatolimod prior to surgery)	50	Change in the number of tumor-infiltrating $CD8^+$ cells

Modified from Procaccio et al. [33]. https://creativecommons.org/licenses/by/4.0/
CRC colorectal cancer

Table 26.4 Adoptive cell therapy study on colorectal cancers

NCT number	Setting	Trial phase	Adoptive cell therapy study	Number of patients	Primary endpoint
NCT03008499	mCRC	I–II	High-activity natural killer versus no special treatment	18	Relief degree of tumors evaluated by RECIST
NCT02577588	mCRC	I	Reactivated T cells	10	DLTs

Modified from Procaccio et al. [33]. https://creativecommons.org/licenses/by/4.0/
mCRC metastatic colorectal cancer, *RECIST* Response Evaluation Criteria In Solid Tumors, *DLT* dose-limiting toxicity

Table 26.5 Cytokine treatment studies on colorectal cancers

NCT number	Setting	Trial phase	Cytokines	Number of patients	Primary endpoint
NCT02415699	Stage III	II–III	DC-CIK + chemotherapy versus chemotherapy	100	DFS
NCT02280278	Stage III	III	Adjuvant CT → CIKCC versus adjuvant CT	550	DFS
NCT01929499	Stages II–III	II	Adjuvant CT + synchronous CIKCC versus adjuvant CT → CIKCC versus adjuvant CT	210	DFS
NCT02466906	Stage III	II	RhGM-CSF versus placebo	60	DFS
Oncolytic virus					
NCT01274624	KRAS	II	REOLYSIN® + FOLFIRI, bevacizumab	32	DLTs
NCT01622543	mCRC	II	FOLFOX + bevacizumab + reolysin versus FOLFOX + bevacizumab	109	PFS

Modified from Procaccio et al. [33]. https://creativecommons.org/licenses/by/4.0/
DC-CIK dendritic cells and cytokine-induced killer cells, *DFS* disease-free survival, *CT* chemotherapy, *CIKCC* cytokine-induced killer cells in colon cancer, *RhGM-CSF* recombinant human granulocyte-macrophage colony-stimulating factor, *FOLFIRI* leucovorin, 5-fluorouracil, and irinotecan, *DLT* dose-limiting toxicity, *FOLFOX* leucovorin, 5-fluorouracil, and oxaliplatin, *PFS* progression-free survival

A phase 2 trial (GOLFIG-1) conducted by Correale et al. evaluated the efficacy of combination of gemcitabine and FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) plus subcutaneous GM-CSF and aldesleukin (GOLFIG regimen) in 46 metastatic colorectal cancer patients reporting prolonging time to progression and improved survival [45]. Based on these findings, a phase 3 trial (GOLFIG-2) performed in 120 metastatic colorectal cancer patients comparing GOLFIG and FOLFOX-4 showed superiority of the GOLFIG regimen in terms of response rate (59% vs. 34%, $p = 0.0001$) and progression-free survival (12.4 months vs. 7.9 months HR: 0.64, $p = 0.0105$) [46]. These results should be confirmed by expanded cohorts.

Checkpoint Inhibitors

Several inhibitory and activatory coreceptors and pathways that control T cell functions in normal physiologic settings have been described and represent a major strategy in cancer immunotherapy.

Immune Checkpoints in Colorectal Cancer

Programmed Cell Death Protein 1 and Its Ligands

Programmed cell death protein 1 (PD-1) is a coinhibitory receptor that inducibly expresses on $CD4^+$ and $CD8^+$ T cells, NKT cells, B cells, and monocytes/macrophages. Ligands of PD-1 include PD-L1 and PD-L2. This pathway has been implicated in tumor immune evasion due to the upregulation of PD-1 on tumor-infiltrating lymphocytes and increased expression of its ligands on tumor cells [47, 48].

Colorectal cancer trials evaluating activity of checkpoint inhibitors did not observe clinical responses. In a phase 1 trial, no responses were observed in 19 colorectal cancer patients treated with nivolumab [49]. Also, in 2012, no response to therapy was seen in 18 colorectal cancer patients using an antagonist of PD-L1 antibody (BMS-936559) [50].

On the other hand, a study demonstrated the association of PD-L1 expression with improved survival in colorectal cancer specimens [51]. This correlation could be demonstrated in a subset of colorectal cancer patients, marked by mismatch repair (MMR)-proficient tumors, whereas no association was found in MMR-deficient colorectal cancer or MSI (microsatellite instability) [52]. This hypothesis that immune checkpoint inhibitors could be more effective in MSI colorectal cancer was further investigated in a phase 2 trial of pembrolizumab, another monoclonal antibody targeting PD-1 [53]. This study showed that MMR status predicted clinical benefit of immune checkpoint blockade with pembrolizumab with enhanced responsiveness in MSI colorectal cancer [53].

CheckMate 142 was a phase 2 study in advanced MSI-H and MSS colorectal cancer patients that evaluated the difference of benefit between nivolumab monotherapy and nivolumab-ipilimumab combination. In MSI-H patients, the overall response rate was 25.5% vs. 33.3%, respectively. An updated result of this study, presented at the American Society of Clinical Oncology (ASCO) 2017, showed in nivolumab patients that objective response rate (ORR), PFS rate, and OS rate were 31%, 48.4%, and 73.8%, respectively [54]. The results were independent from PD-L1 expression, BRAF, KRAS mutation status, and history of Lynch syndrome. The results, further updated in 2018, showed that complete responses increased from 3% to 9%. Progression-free survival reached a plateau, which may show the durable response with this molecule [55].

In a phase 1b/2 study of RAS wild-type patients, cetuximab (400 mg/m^2 loading dose with a weekly maintenance of 250 mg/ m^2) in combination with pembrolizumab (200 mg every 3 weeks) was tested in 9 metastatic colorectal cancer patients [56]. Hypomagnesemia, rash, urticaria, hypocalcemia, ascites, and alkaline phosphatase (ALP) increase were reported as grade 3 adverse events. In 6 patients, a stabile disease was achieved for more than 16 weeks. The results are expected to be further confirmed in a phase 2 study.

Cytotoxic T Lymphocyte Antigen-4 and B7

Another molecule involved in T lymphocyte inhibition is cytotoxic T lymphocyte antigen-4 (CTLA-4), that is expressed on the surface of T cells. CTLA-4 has affinity for B7-1 and B7-2, costimulatory receptors on antigen-presenting cells, and this interaction transmits inhibitory signals to attenuate T cell activation [47].

The inhibition of T cell activation also results in the reduction of Tregs. Since Tregs accumulation has been linked with poor prognosis in colorectal cancer, this could be an interesting therapeutic strategy for blockade of CTLA-4 in colorectal cancer [57].

Tremelimumab, a similar antibody to ipilimumab (the first anti-CTLA-4 approved by the US Food and Drug Administration [FDA]), has been investigated in a phase 2 study for patients with refractory metastatic colorectal cancer. Unfortunately, only 1 patient received a second dose, whereas the remaining 46 patients had disease progression or disease-related death before receiving the planned second dose at 3 months [58]. Phase 1 trials are ongoing in combination with durvalumab, a monoclonal antibody against PD-L1, in patients with solid tumors (NCT01975831).

Lymphocyte Activation Gene-3

The lymphocyte activation gene-3 (LAG-3), also known as CD223, is a receptor of cell surface of the immunoglobulin family. Through its interaction with MHC class II, LAG-3 plays a transcendental role in downregulation of cell proliferation of activated T cells, NK cells, B cells, and dendritic cells [59, 60].

Together with CD49b expression, the co-expression of LAG-2 marks highly suppressive human type 1 regulatory T cells (Tr1), a subgroup of Tregs producing IL-10 [61]. Also, it has demonstrated that the co-expression of multiple inhibitory receptors, such as the combination with PD-1, was associated with a major T cell exhaustion. Then, the simultaneous inhibition of PD-1 and LAG-3 could enhance T effector activity as compared to either molecule alone [62]. An analysis of 108 colorectal cancer tissues and their respective non-malignant peritumoral tissues showed an increase in number of cells expressing LAG-3/CD49b in tumoral tissues as compared with non-malignant peritumoral tissues [63]. These observations justify ongoing phase 1 trials with this molecular target.

T Cell Immunoglobulin and Mucin Containing Protein-3

T cell immunoglobulin and mucin containing protein-3 (TIM-3) is expressed on IFN-γ(gamma) producing CD4 Th1$^+$ and CD8 cytotoxic T cells. Through its ligand, galectin-9, TIM-3 is believed to play an important role in inhibiting Th1 response and inducing cell death [64]. Furthermore, animal models have demonstrated its role in T cell exhaustion due to the expression of TIM-3, with PD-1, in the most suppressed or dysfunctional populations of CD8 T cells in hematological and solid malignancies [64].

It was observed that in peripheral blood samples from colorectal cancer patients, there were higher levels of circulating TIM-3/PD-1 CD8$^+$ T cells compared to healthy subjects. Likewise, an increase of TIM-3/PD-1 CD8$^+$ T cells was shown in colorectal cancer tissues, when compared with healthy adjacent peritumoral tissues. Moreover, distinguishing the subset of T cells by the expression of PD-1 demonstrated a significant lower level of IFN-γ(gamma) production in the PD-1 subset. Together with the lack of objective responses by PD-1 blockade in colorectal cancer patients, these results suggest TIM-3 as a more dominant inhibitory receptor, restricting T cell response in colorectal cancer patients [64].

There are clinical trials that are testing anti-TIM-3 or anti-LAG-3 blockade in monotherapy and in combination (NCT02817633, NCT01968109).

CD70 and CD27

CD70, a member of the tumor necrosis factor family, is expressed for activated T and B cells and mature dendritic cells; however, constitutive expression of CD70 in malignant cells has been described [65]. Through the interaction with its ligand, CD27, the upregulation of CD70 allows the evasion of immune system by three mechanisms: (1) induction of T cell apoptosis, (2) skewing T cells toward T cell exhaustion, and (3) increasing suppressive Tregs [66]. In vivo trials demonstrated evasion of immune surveillance by recruitment of CD27$^+$ Treg to the tumor site [67].

The role of CD70-mediated immunoescape was demonstrated in non-small cell lung cancer, where CD27$^+$ lymphocytes were found in the tumor microenvironment with a trend toward increased Foxp3 expression and higher CD4/CD8 ratios surrounding CD70$^+$ malignant cells [68].

Although the expression of CD70 has not been described in colorectal tumors, unpublished data of Jacobs et al. found expression of CD70 in 6 of 28 biopsies [21].

Otherwise, other groups focus the strategy on the immunostimulatory potential of a CD27-agonistic monoclonal antibody, such as varlilumab. CD27 belongs to the tumor necrosis factor receptor superfamily and plays a critical role in immunological processes, such as T cell survival, T cell activation, and the cytotoxic activity of NK cells [69] . Furthermore, ligation of CD27 by CD70 has shown stimulatory effects on T cell proliferation, expansion, and survival dependent upon IL-2 autocrine signaling.

Glucocorticoid-Induced TNFR-Related Protein

Also known as CD357, glucocorticoid-induced TNFR-related protein (GITR) is a surface receptor molecule that has been shown to be involved in inhibiting the suppressive activity of Treg and extending the survival of T effector cells. This molecule may be a great promise for the agonistic antibodies in immunotherapy [70].

GITRL, its unique ligand, is expressed on activated antigen-presenting cells, and the interaction of them provides costimulation of effector T lymphocytes [71]. Studies in animal models showed that GITR agonistic molecules (like DTA-1) can mediate tumor regression mediated by the loss of lineage stability of Tregs, reducing its suppressive influence in the tumor microenvironment [72].

Schaer et al. reported a tumor-specific T cell response comprised by high numbers of activated Tregs expressing high levels of GITR, in colorectal cancer patients with liver metastases. The treatment with GITRL produced inhibition of Treg-mediated suppression, preventing hyporesponsiveness of T cells [72].

OX40 (CD134)

OX40 (TNR4 or CD134) is another member of the tumor necrosis factor superfamily, similar to GITR and 4-1BB, and its engagement promotes T cell activation, survival, proliferation and cytokine production [73]. This molecule is primarily expressed on activated CD4 T cells and on CD8 T cells, neutrophils, dendritic cells, and Tregs [74]. Its ligand, OX40L, is most common in antigen-presenting cells, additionally found on activated T cells and B cells [75]. OX40 expression is induced by T cell receptor stimulation, but costimulation via other molecules, such as CD28, or exposure to cytokines can further upregulate expression [76] .

OX40 agonism has been evaluated in preclinical models, as a monotherapy, which has resulted in delayed tumor growth in vivo and promoted the rejection of various tumors [77]. OX40-dependent antitumor immunity required both CD4 and CD8 T cells. Combinations of anti-OX40 with fractionated radiotherapy, IL-12 and anti-4-1BB, anti-CTLA-4 and CpG oligonucleotides, anti-CD25 and anti-CTLA-4 with adoptive cell transfer, transforming growth factor β (beta) inhibition, or IL-2 improved antitumor responses, tumor rejection, long-term survival, resistance to tumor rechallenge in mice bearing various cancers [76, 78–82].

In the first phase 1 clinical trial, 30 patients received a murine anti-human OX40 monoclonal antibody; regression was reported of at least 1 metastatic lesion in 12 patients after a single dose [83]. Despite these positive results, it is unlikely that anti-OX40 alone will be sufficient to induce complete response, since antitumor immunity is directed by a dynamic constellation of signals. Perhaps a better benefit could be achieved in combination with other agents such as antagonistics antibodies, such as PD-L1 (durvalumab and atezolizumab) and CTLA-4 (tremelimumab).

Although not reported yet, in the NCT01644968 phase I study, anti-OX40 monoclonal antibody reached efficacy. The NCT02205333 study is recruiting patients for testing this molecule in combination with anti-CTLA-4 and anti-PD-1 agents.

4-1BB

4-1BB (or CD137) is a molecule with effects on T cell proliferation and CD8 T cell function [84]. It is expressed on activated but not resting T cells, activated natural killer cells, natural killer T cells, and is expressed constitutively on some population of dendritic cells and Tregs [85].

Stimulation of 4-1BB by its ligand (4-1BBL) or by agonist antibodies enhances the activation of several immune cells, including T cells, dendritic cells (upregulation of B7 molecules and immunostimulatory cytokine production), monocytes, and neutrophils, and induces a spectrum of effects on B and NK cells [86].

Preclinical trials showed that targeting 4-1BB with an agonist antibody can promote tumor control in several preclinical models and is frequently associated with increase cytotoxic T lymphocyte effector capability [87, 88].

Correlation between 4-1BB positivity in peripheral blood samples and colorectal cancer stage and invasion depth has been reported by Cepowicz et al. [89]. Moreover, expression of its ligand was shown to be lower in malignant colonic tissue compared with paired normal tissue [90]. The efficacy of 4-1BB agonistic agents for the treatment of colorectal cancer with liver metastases has been proved in preclinical animal models [91].

There are two agonistic antibodies in clinical development, with phase 1 trials: urelumab and PF-05082566. A case of fatal hepatotoxicity was reported with urelumab in a trial in metastatic melanoma, so this study was terminated. For PF-05082566 no significant hepatotoxicity has been reported to date [92].

4-1BB is upregulated on human NK cells when they encounter antibody-bound tumor cells; moreover, increased levels of 4-1BB on circulating and intratumoral NK cells were directly correlated to an increase in epidermal growth factor receptor (EGFR)-specific CD8 T cells, and the combination with cetuximab marked clear synergism, shown by the complete response of the tumor and prolonged survival [93, 94].

In the NCT00309023 study, the activity of anti-4-1BB antibody was shown. However, the phase 2 study was terminated early due to advanced toxicity. The same agent in lower doses is still being tested in the NCT02253922 trial in combination with PD-1 blockade.

CD40

CD40 is a member of the tumor necrosis factor receptor superfamily, which was initially characterized on B cells and is also expressed on dendritic cells, monocytes, platelets, and macrophages as well as by non-hematopoietic cells such as myofibroblasts, fibroblasts, and epithelial and endothelial cells. Its ligand, known as CD154 or CD40L, is expressed primarily by activated T cells as well as activated B cells and platelets [95].

The interaction with its ligand, CD40L, on activated Th cells enhances the presentation and expression of costimulatory molecules, licensing dendritic cells to mature and achieve all of the necessary characteristics to effectively trigger T cell activation. In animal models, engagement with CD40L promoted cytokine production and enabled effective T cell activation and differentiation [96, 97].

In colorectal cancer, expression of CD40 has been demonstrated [98]. The use of CD40 as a prognostic tool in other malignancies has been demonstrated, although further studies to elucidate its role in colorectal cancer are necessary [99].

Clinical trials with agonistic CD40 monoclonal antibodies have demonstrated clinical activity in absence of relevant toxicity. However, response rates remain 20% or less, such that CD40 agonists may be more effective in combination with chemotherapy, vaccines, or inhibitory checkpoint molecules such as anti-CTLA-4 or anti-PD-L1 monoclonal antibodies [100].

Role of Colorectal Cancer Biomarkers in Immunomodulation

Despite the recent development of new strategies in therapy of colorectal cancer, with genetic profiling of individual tumors and new agents with better toxicity profiles, the selection of patients and individualized treatment remains challenging. In this setting, identification of genetic factors that could influence tumor microenvironment is essential to improve the selection of a specific therapy strategy.

Lal et al. carried out a bioinformatics analysis of colorectal cancer data in The Cancer Genome Atlas involving 2-dimensional hierarchical clustering to define an immune signature that was used to characterize the immune response across key patient groups [101]. An immune signature termed the Co-ordinate Immune Response Cluster (CIRC) comprising 28 genes was coordinately regulated across the patient population. This included essentially all class II MHC loci, whereas expressions of class I MHC were excluded. Additionally, the major immune checkpoint molecules (PD-L1, PD-L2, LAG-3, TIM-3, CTLA-4) were included [101].

Microsatellite Instability

MSI-high (MSI-H), which is the molecular fingerprint of a deficient DNA mismatch repair system and linked to a high mutational burden, was associated with a high immune infiltration by Th cells and class II-related genes, chemokines, and immune inhibitory checkpoint molecules. Similarly, POL mutations were linked with high mutational burden and high immune infiltration, but the coordinate expression of inhibitory pathways observed suggests that the combination checkpoint blockade therapy may be required to improve efficacy [101].

The MSI-H group of patients were shown to derive the benefit from immune checkpoint inhibition; however, in microsatellite-stable patients, there could be a small benefit. Since then, there are efforts to show a better predictive biomarker to target besides the MSI status. In this context, "immunoscore" was developed. The immunoscore is a scoring system based on density of CD3- and CD8-positive T cells and CD3/CD45RO-positive T memory cells in tumoral center and invasive margin. A scoring from low density (score: 0) to highest immune infiltration (score: 4) is used. Higher scores are correlated with higher PD-L1 levels and derive benefit from standard chemotherapy. In addition, immunoscore is more predictive for response to chemotherapy than MSI status. Recent studies are conducted to show the same predicity for immunotherapies [102]. At the same time, patients with immunoscores of 3–4 have higher immune infiltrates and might have longer disease-specific recurrence-free intervals independent of MSI status [102, 103].

KRAS

RAS mutation predicts for a relatively poor immune infiltration and low inhibitory molecule expression. KRAS- and NRAS-mutated colorectal cancers have lowered levels of CD4 T cells. In this setting, therapy with checkpoint blockade may be less efficacious, highlighting a requirement for novel strategies in this patient group [101].

BRAF

Mutations in BRAF have been described in 5–15% of colorectal cancer patients and are frequently found in MSI-high tumors. BRAF mutation is associated with worse survival in microsatellite stability tumors, but its role in MSI-high tumors is uncertain. Probably the poor prognosis does not depend only on the BRAF status; the mutation might have different effects depending on the type of genetic pathway in which it is produced [104]. Recent data indicates that melanomas bearing mutant BRAF may also have altered immune responses, suggesting additional avenues for treatment of these patients [105]. Combination of BRAF inhibitors with new immunotherapies such as checkpoint blockade antibodies might further enhance immune activation.

Conclusion

In the last few years, there has been important progress in understanding the role of the immune system in the fight against cancer. These recent advances open the door to a range of therapeutic options with important benefits for patients suffering from this malignant disease. The complex role of the immune system and its particular physiological distribution in the digestive system, especially the colon and small intestine, is a challenge in the research and develop-

ment of new therapies that would be effective to treat cancer. Probably, given the significant interaction between tumor cells, the immune system, and the tumor microenvironment, the best therapeutic strategy will be a combination of cytotoxic treatment, biological drugs, and immune-modulating drugs, perhaps including a strategy combining vaccines with these agents. Despite the evidence of the activity of these agents in stimulating the immune system in MMR-deficient colorectal cancer, with its high mutational burden, it is not possible to establish a definitive role in this subgroup of patients. There are many ongoing trials that will help us in the understanding of this complex interaction between the immune system and cancer, so we should not hesitate to continue the research that allows us to offer better therapeutic strategies and quality of life for our patients.

References

1. Bray F, Ren JS, Masuyer E FJ. GLOBOCAN 2012 v1.0. International Agency for Research on Cancer, World Health Organization, Lyon, France; 2013. http://globocan.iarc.fr/Default.aspx Accessed 18 Mar 2016.
2. Las Cifras del Cáncer en España en 2016. Accessed 18 Mar 2016. http://seom.org/seomcms/images/stories/recursos/LA_CIFRAS_DEL_CANCER_EN_2016.pdf.
3. American Cancer Society. Colorectal cancer facts & figures 2014–2016. Atlanta: American Cancer Society. 2014. Accessed 18 Mar 2016. http://www.cancer.org/acs/groups/content/documents/document/acspc-042280.pdf.
4. Hellinger MD, Santiago CA. Reoperation for recurrent colorectal cancer. Clin Colon Rectal Surg. 2006;19(4):228–36.
5. Kocián P, Šedivcová M, Drgáč J, Cerná K, Hoch J, Kodet R, et al. Tumor-infiltrating lymphocytes and dendritic cells in human colorectal cancer: their relationship to KRAS mutational status and disease recurrence. Hum Immunol. 2011;72(11):1022–8.
6. Gonzalez-Pons M, Cruz-Correa M. Colorectal cancer biomarkers: where are we now? Biomed Res Int. 2015;2015:149014.
7. Deschoolmeester V, Baay M, Specenier P, Lardon F, Vermorken JB. A review of the most promising biomarkers in colorectal cancer: one step closer to targeted therapy. Oncologist AlphaMed Press. 2010;15(7):699–731.
8. Pernot S, Terme M, Voron T, Colussi O, Marcheteau E, Tartour E, et al. Colorectal cancer and immunity: what we know and perspectives. World J Gastroenterol. 2014;20(14):3738–50.
9. Frisch M. Association of cancer with AIDS-related immunosuppression in adults. JAMA. 2001;285(13):1736–45.
10. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, et al. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature. 2001;410(6832):1107–11.
11. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3(11):991–8.
12. Markman JL, Shiao SL. Impact of the immune system and immunotherapy in colorectal cancer. J Gastrointest Oncol. 2015;6(1):208–23.
13. Malmberg K-J, Bryceson YT, Carlsten M, Andersson S, Björklund A, Björkström NK, et al. NK cell-mediated targeting of human cancer and possibilities for new means of immunotherapy. Cancer Immunol Immunother. 2008;57(10):1541–52.
14. Carbone E, Neri P, Mesuraca M, Fulciniti MT, Otsuki T, Pende D, et al. HLA class I, NKG2D, and natural cytotoxicity receptors regulate multiple myeloma cell recognition by natural killer cells. Blood Am Soc Hematol. 2005;105(1):251–8.
15. Terme M, Fridman WH, Tartour E. NK cells from pleural effusions are potent antitumor effector cells. Eur J Immunol. 2013;43(2):331–4.
16. Coca S, Perez-Piqueras J, Martinez D, Colmenarejo a SM a, Vallejo C, et al. The prognostic significance of intratumoral natural killer cells in patients with colorectal carcinoma. Cancer. 1997;79(12):2320–8.
17. Tachibana T, Onodera H, Tsuruyama T, Mori A, Nagayama S, Hiai H, et al. Increased intratumor Valpha24-positive natural killer T cells: a prognostic factor for primary colorectal carcinomas. Clin Cancer Res. 2005;11(20):7322–7.
18. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer. 2004;4(1):71–8.
19. Edin S, Wikberg ML, Rutegård J, Oldenborg P-A, Palmqvist R. Phenotypic skewing of macrophages in vitro by secreted factors from colorectal cancer cells. PLoS One. 2013;8(9):e74982.
20. Erreni M, Mantovani A, Allavena P. Tumor-associated macrophages (TAM) and inflammation in colorectal cancer. Cancer Microenviron. 2011;4(2):141–54.
21. Jacobs J, Smits E, Lardon F, Pauwels P, Deschoolmeester V. Immune checkpoint modulation in colorectal cancer: what's new and what to expect. J Immunol Res. 2015;2015:158038.
22. Golubovskaya V, Wu L. Different subsets of T cells, memory, effector functions, and CAR-T immunotherapy. Cancers (Basel). 8(3).
23. Obermajer N, Dahlke MH. (Compl)Ex-Th17-Treg cell interrelationship. Oncoimmunology. 2015;5(1):e1040217.
24. Yao Y, Jiang Q, Jiang L, Wu J, Zhang Q, Wang J, et al. Lnc-SGK1 induced by Helicobacter pylori infection and highsalt diet promote Th2 and Th17 differentiation in human gastric cancer by SGK1/Jun B signaling. Oncotarget. 2016;7(15):20549–60.
25. Amin M, Lockhart AC. The potential role of immunotherapy to treat colorectal cancer. Expert Opin Investig Drugs. 2015;24(3):329–44.
26. Mocellin S, Rossi CR, Lise M, Nitti D. Colorectal cancer vaccines: principles, results, and perspectives. Gastroenterology. 2004;127(6):1821–37.
27. Blankenstein T, Coulie PG, Gilboa E, Jaffee EM. The determinants of tumour immunogenicity. Nat Rev Cancer. 2012;12(4):307–13.
28. Keenan BP, Jaffee EM. Whole cell vaccines--past progress and future strategies. Semin Oncol. 2012;39(3):276–86.
29. Koido S, Ohkusa T, Homma S, Namiki Y, Takakura K, Saito K, et al. Immunotherapy for colorectal cancer. World J Gastroenterol. 2013;19(46):8531–42.
30. Hoover HC, Brandhorst JS, Peters LC, Surdyke MG, Takeshita Y, Madariaga J, et al. Adjuvant active specific immunotherapy for human colorectal cancer: 6.5-year median follow-up of a phase III prospectively randomized trial. J Clin Oncol. 1993;11(3):390–9.
31. Harris J, Ryan L, Hoover H, Stuart R, Oken M, Benson A, et al. Adjuvant active specific immunotherapy for stage II and III colon cancer with an autologous tumor cell vaccine: Eastern Cooperative Oncology Group Study E5283. J Clin Oncol. 2000;18(1):148–57.
32. Vermorken J, Claessen A, van Tinteren H, Gall H, Ezinga R, Meijer S, et al. Active specific immunotherapy for stage II and stage III human colon cancer: a randomised trial. Lancet. 1999;353(9150):345–50.
33. Procaccio L, Schirripa M, Fassan M, Vecchione L, Bergamo F, Prete AA, et al. Immunotherapy in gastrointestinal cancers. Biomed Res Int. 2017;2017:4346576.
34. Moulton HM, Yoshihara PH, Mason DH, Iversen PL, Triozzi PL. Active specific immunotherapy with a {beta}-human chorionic gonadotropin peptide vaccine in patients with metastatic colorectal cancer: antibody response is associated with improved survival. Clin Cancer Res. 2002;8(7):2044–51.
35. Bilusic M, Heery CR, Arlen PM, Rauckhorst M, Apelian D, Tsang KY, et al. Phase I trial of a recombinant yeast-CEA vaccine

(GI-6207) in adults with metastatic CEA-expressing carcinoma. Cancer Immunol Immunother. 2014;63(3):225–34.
36. Posner MC, Niedzwiecki D, Venook AP, Hollis DR, Kindler HL, Martin EW, et al. A phase II prospective multi-institutional trial of adjuvant active specific immunotherapy following curative resection of colorectal cancer hepatic metastases: cancer and leukemia group B study 89903. Ann Surg Oncol. 2008;15(1):158–64.
37. Miyagi Y, Imai N, Sasatomi T, Yamada A, Mine T, Katagiri K, et al. Induction of cellular immune responses to tumor cells and peptides in colorectal cancer patients by vaccination with SART3 peptides. Clin Cancer Res. 2001;7(12):3950–62.
38. Speetjens FM, Kuppen PJK, Welters MJP, Essahsah F, Voet van den Brink AMEG, Lantrua MGK, et al. Induction of p53-specific immunity by a p53 synthetic long peptide vaccine in patients treated for metastatic colorectal cancer. Clin Cancer Res. 2009;15(3):1086–95.
39. Kimura T, McKolanis JR, Dzubinski LA, Islam K, Potter DM, Salazar AM, et al. MUC1 vaccine for individuals with advanced adenoma of the colon: a cancer immunoprevention feasibility study. Cancer Prev Res (Phila). 2013;6(1):18–26.
40. denoue S, Hirohashi Y, Torigoe T, Sato Y, Tamura Y, Hariu H, et al. A potent immunogenic general cancer vaccine that targets survivin, an inhibitor of apoptosis proteins. Clin Cancer Res. 2005;11(4):1474–82.
41. Schulze T, Kemmner W, Weitz J, Wernecke KD, Schirrmacher V, Schlag PM. Efficiency of adjuvant active specific immunization with Newcastle disease virus modified tumor cells in colorectal cancer patients following resection of liver metastases: results of a prospective randomized trial. Cancer Immunol Immunother. 2009;58(1):61–9.
42. Karlsson M, Marits P, Dahl K, Dagöö T, Enerbäck S, Thörn M, et al. Pilot study of sentinel-node-based adoptive immunotherapy in advanced colorectal cancer. Ann Surg Oncol. 2010;17(7):1747–57.
43. Zhen Y-H, Liu X-H, Yang Y, Li B, Tang J-L, Zeng Q-X, et al. Phase I/II study of adjuvant immunotherapy with sentinel lymph node T lymphocytes in patients with colorectal cancer. Cancer Immunol Immunother. 2015;64:1083–93.
44. Parkhurst MR, Yang JC, Langan RC, Dudley ME, Nathan D-AN, Feldman SA, et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. Mol Ther. 2011;19(3):620–6.
45. Correale P, Tagliaferri P, Fioravanti A, Del Vecchio MT, Remondo C, Montagnani F, et al. Immunity feedback and clinical outcome in colon cancer patients undergoing chemoimmunotherapy with gemcitabine + FOLFOX followed by subcutaneous granulocyte macrophage colony-stimulating factor and aldesleukin (GOLFIG-1 Trial). Clin Cancer Res. 2008;14(13):4192–9.
46. Correale P, Botta C, Rotundo MS, Guglielmo A, Conca R, Licchetta A, et al. Gemcitabine, oxaliplatin, levofolinate, 5-fluorouracil, granulocyte-macrophage colony-stimulating factor, and interleukin-2 (GOLFIG) versus FOLFOX chemotherapy in metastatic colorectal cancer patients: the GOLFIG-2 multicentric open-label randomized phase. J Immunother. 2014;37(1):26–35.
47. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2005;23:515–48.
48. Rozali EN, Hato SV, Robinson BW, Lake RA, Lesterhuis WJ. Programmed death ligand 2 in cancer-induced immune suppression. Clin Dev Immunol. 2012;2012:656340.
49. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54.
50. Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–65.
51. Droeser RA, Hirt C, Viehl CT, Frey DM, Nebiker C, Huber X, et al. Clinical impact of programmed cell death ligand 1 expression in colorectal cancer. Eur J Cancer. 2013;49(9):2233–42.
52. Heinimann K. Toward a molecular classification of colorectal cancer: the role of microsatellite instability status. Front Oncol. 2013;3:272.
53. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–20.
54. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017;18(9):1182–91.
55. Overman MJ, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol. 2018;36(8):773–9.
56. Boland PM, Hutson A, Maguire O, Minderman H, Fountzilas C, Iyer RV. A phase Ib/II study of cetuximab and pembrolizumab in RAS-wt mCRC. J Clin Oncol. 2018;36. (suppl 4S; abstr 834).
57. Betts G, Jones E, Junaid S, El-Shanawany T, Scurr M, Mizen P, et al. Suppression of tumour-specific $CD4^+$ T cells by regulatory T cells is associated with progression of human colorectal cancer. Gut. 2012;61(8):1163–71.
58. Chung KY, Gore I, Fong L, Venook A, Beck SB, Dorazio P, et al. Phase II study of the anti-cytotoxic T-lymphocyte-associated antigen 4 monoclonal antibody, tremelimumab, in patients with refractory metastatic colorectal cancer. J Clin Oncol. 2010;28(21):3485–90.
59. Goldberg MV, Drake CG. LAG-3 in cancer immunotherapy. Curr Top Microbiol Immunol. 2011;344:269–78.
60. Shin DS, Ribas A. The evolution of checkpoint blockade as a cancer therapy: what's here, what's next? Curr Opin Immunol. 2015;33:23–35.
61. Gagliani N, Magnani CF, Huber S, Gianolini ME, Pala M, Licona-Limon P, et al. Coexpression of CD49b and LAG-3 identifies human and mouse T regulatory type 1 cells. Nat Med. 2013;19(6):739–46.
62. Blackburn SD, Shin H, Haining WN, Zou T, Workman CJ, Polley A, et al. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. Nat Immunol. 2009;10(1):29–37.
63. Chen J, Chen Z. The effect of immune microenvironment on the progression and prognosis of colorectal cancer. Med Oncol. 2014;31(8):82.
64. Zhu C, Anderson AC, Schubart A, Xiong H, Imitola J, Khoury SJ, et al. The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. Nat Immunol. 2005;6(12):1245–52.
65. Denoeud J, Moser M. Role of CD27/CD70 pathway of activation in immunity and tolerance. J Leukoc Biol. 2011;89(2):195–203.
66. Jacobs J, Deschoolmeester V, Zwaenepoel K, Rolfo C, Silence K, Rottey S, et al. CD70: an emerging target in cancer immunotherapy. Pharmacol Ther. 2015;155:1–10.
67. Claus C, Riether C, Schürch C, Matter MS, Hilmenyuk T, Ochsenbein AF. CD27 signaling increases the frequency of regulatory T cells and promotes tumor growth. Cancer Res. 2012;72(14):3664–76.
68. Jacobs J, Zwaenepoel K, Rolfo C, Van den BJ, Deben C, Silence K, et al. Unlocking the potential of CD70 as a novel immunotherapeutic target for non-small cell lung cancer. Oncotarget. 2015;6:13462–75.
69. Thomas LJ, He L-Z, Marsh H, Keler T. Targeting human CD27 with an agonist antibody stimulates T-cell activation and antitumor immunity. Oncoimmunology. 2014;3(1):e27255.

70. Schaer DA, Hirschhorn-Cymerman D, Wolchok JD, Hodi F, O'Day S, McDermott D, et al. Targeting tumor-necrosis factor receptor pathways for tumor immunotherapy. J Immunother Cancer. 2014;2(1):7.
71. Pedroza-Gonzalez A, Verhoef C, Ijzermans JNM, Peppelenbosch MP, Kwekkeboom J, Verheij J, et al. Activated tumor-infiltrating CD4+ regulatory T cells restrain antitumor immunity in patients with primary or metastatic liver cancer. Hepatology. 2013;57(1):183–94.
72. Schaer DA, Budhu S, Liu C, Bryson C, Malandro N, Cohen A, et al. GITR pathway activation abrogates tumor immune suppression through loss of regulatory T-cell lineage stability. Cancer Immunol Res. 2013;1(5):320–31.
73. Weinberg AD, Morris NP, Kovacsovics-Bankowski M, Urba WJ, Curti BD. Science gone translational: the OX40 agonist story. Immunol Rev. 2011;244(1):218–31.
74. Takeda I, Ine S, Killeen N, Ndhlovu LC, Murata K, Satomi S, et al. Distinct roles for the OX40-OX40 ligand interaction in regulatory and nonregulatory T cells. J Immunol. 2004;172(6):3580–9.
75. Cepowicz D, Zaręba K, Gryko M, Stasiak-Bermuta A, Kędra B. Determination of the activity of CD134 (OX-40) and CD137 (4-1BB) adhesive nolecules by means of flow cytometry in patients with colorectal cancer metastases to the liver. Polish J Surg. 2011;83(8):424–9.
76. Redmond WL, Triplett T, Floyd K, Weinberg AD, Watts T, Croft M, et al. Dual anti-OX40/IL-2 therapy augments tumor immunotherapy via IL-2R-mediated regulation of OX40 expression. PLoS One. 2012;7(4):e34467.
77. Weinberg AD, Rivera M-M, Prell R, Morris A, Ramstad T, Vetto JT, et al. Engagement of the OX-40 receptor in vivo enhances antitumor immunity. J Immunol. 2000;164(4):2160–9.
78. Gough MJ, Crittenden MR, Sarff M, Pang P, Seung SK, Vetto JT, et al. Adjuvant therapy with agonistic antibodies to CD134 (OX40) increases local control after surgical or radiation therapy of cancer in mice. J Immunother. 2010;33(8):798–809.
79. Pan P-Y, Zang Y, Weber K, Meseck ML, Chen S-H. OX40 ligation enhances primary and memory cytotoxic T lymphocyte responses in an immunotherapy for hepatic colon metastases. Mol Ther. 2002;6(4):528–36.
80. Houot R, Levy R. T-cell modulation combined with intratumoral CpG cures lymphoma in a mouse model without the need for chemotherapy. Blood. 2009;113(15):3546–52.
81. Watanabe A, Hara M, Chosa E, Nakamura K, Sekiya R, Shimizu T, et al. Combination of adoptive cell transfer and antibody injection can eradicate established tumors in mice–an in vivo study using anti-OX40mAb, anti-CD25mAb and anti-CTLA4mAb-. Immunopharmacol Immunotoxicol. 2010;32(2):238–45.
82. Garrison K, Hahn T, Lee W-C, Ling LE, Weinberg AD, Akporiaye ET. The small molecule TGF-β signaling inhibitor SM16 synergizes with agonistic OX40 antibody to suppress established mammary tumors and reduce spontaneous metastasis. Cancer Immunol Immunother. 2012;61(4):511–21.
83. Curti BD, Kovacsovics-Bankowski M, Morris N, Walker E, Chisholm L, Floyd K, et al. OX40 is a potent immune-stimulating target in late-stage cancer patients. Cancer Res. 2013;73(24):7189–98.
84. Shuford WW, Klussman K, Tritchler DD, Loo DT, Chalupny J, Siadak AW, et al. 4-1BB costimulatory signals preferentially induce CD8+ T cell proliferation and lead to the amplification in vivo of cytotoxic T cell responses. J Exp Med. 1997;186(1):47–55.
85. Vinay DS, Kwon BS. 4-1BB signaling beyond T cells. Cell Mol Immunol. 2011;8(4):281–4.
86. Vinay DS, Kwon BS. Immunotherapy of cancer with 4-1BB. Mol Cancer Ther. 2012;11(5):1062–70.
87. Melero I, Shuford WW, Newby SA, Aruffo A, Ledbetter JA, Hellström KE, et al. Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. Nat Med. 1997;3(6):682–5.
88. Sabel MS, Conway TF, Chen FA, Bankert RB. Monoclonal antibodies directed against the T-cell activation molecule CD137 (interleukin-A or 4-1BB) block human lymphocyte-mediated suppression of tumor xenografts in severe combined immunodeficient mice. J Immunother. 2000;23(3):362–8.
89. Cepowicz D, Gryko M, Zaręba K, Stasiak-Bermuta A, Kędra B. Assessment of activity of an adhesion molecule CD134 and CD137 in colorectal cancer patients. Polish J Surg. 2011;83(12):641–5.
90. Dimberg J, Hugander A, Wågsäter D. Expression of CD137 and CD137 ligand in colorectal cancer patients. Oncol Rep. 2006;15(5):1197–200.
91. Chen S. Rejection of disseminated metastases of colon carcinoma by synergism of IL-12 gene therapy and 4-1BB costimulation. Mol Ther. 2000;2(1):39–46.
92. Segal NH, Gopal AK, Shailender B, Kohrt HE, Levy R, Pishvain MJ, et al. A phase 1 study of PF-05082566 (anti-4-1BB) in patients with advanced cancer. J Clin Oncol. 2014;32:5s.. (suppl; abstr 3007)
93. Kohrt HE, Colevas AD, Houot R, Weiskopf K, Goldstein MJ, Lund P, et al. Targeting CD137 enhances the efficacy of cetuximab. J Clin Invest. 2014;124(6):2668–82.
94. Houot R, Kohrt H. CD137 stimulation enhances the vaccinal effect of anti-tumor antibodies. Oncoimmunology. 2014;3(7):e941740.
95. Elgueta R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle RJ. Molecular mechanism and function of CD40/CD40L engagement in the immune system. Immunol Rev. 2009;229(1):152–72.
96. Barth RJ, Fisher DA, Wallace PK, Channon JY, Noelle RJ, Gui J, et al. A randomized trial of ex vivo CD40L activation of a dendritic cell vaccine in colorectal cancer patients: tumor-specific immune responses are associated with improved survival. Clin Cancer Res. 2010;16(22):5548–56.
97. Honeychurch J, Cheadle EJ, Dovedi SJ, Illidge TM. Immunoregulatory antibodies for the treatment of cancer. Expert Opin Biol Ther. 2015;15(6):787–801.
98. Georgopoulos NT, Merrick A, Scott N, Selby PJ, Melcher A, Trejdosiewicz LK. CD40-mediated death and cytokine secretion in colorectal cancer: a potential target for inflammatory tumour cell killing. Int J Cancer. 2007;121(6):1373–81.
99. Palmer DH, Hussain SA, Ganesan R, Cooke PW, Wallace DMA, Young LS, et al. CD40 expression in prostate cancer: a potential diagnostic and therapeutic molecule. Oncol Rep. 2004;12(4):679–82.
100. Vonderheide RH, Glennie MJ. Agonistic CD40 antibodies and cancer therapy. Clin Cancer Res. 2013;19(5):1035–43.
101. Lal N, Beggs AD, Willcox BE, Middleton GW. An immunogenomic stratification of colorectal cancer: implications for development of targeted immunotherapy. Oncoimmunology. 2015;4(3):e976052.
102. Mlecnik B, Bindea G, Angell HK, et al. Integrative analyses of colorectal cancer show immunoscore is a stronger predictor of patient survival than microsatellite instability. Immunity. 2016;44(3):698–711.
103. Galon J, Pages F, Marincola FM, Angell HK, Thurin M, Lugli A, et al. Cancer classification using the Immunoscore: a worldwide task force. J Transl Med. 2012;10:205.
104. Deschoolmeester V, Smits E, Peeters M, Vermorken JB. Status of active specific immunotherapy for stage II, stage III, and resected stage IV colon cancer. Curr Colorectal Cancer Rep. 2013;9(4):380–90.
105. Ilieva KM, Correa I, Josephs DH, Karagiannis P, Egbuniwe IU, Cafferkey MJ, et al. Effects of BRAF mutations and BRAF inhibition on immune responses to melanoma. Mol Cancer Ther. 2014;13(12):2769–83.
106. Fields AL, Keller A, Schwartzberg L, Bernard S, Kardinal C, Cohen A, Schulz J, Eisenberg P, Forster J, Wissel P. Adjuvant therapy with the monoclonal antibody Edrecolomab plus fluorouracil-based therapy does not improve overall survival of patients with stage III colon cancer. J Clin Oncol. 2009;27(12):1941–7.

Novel Targeted Treatment Approaches in Pancreatic Cancer

27

Maria Diab, Muhammad Saad Hamid,
Ramzi M. Mohammad, Philip A. Philip, and Asfar S. Azmi

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains the fourth leading cause of cancer-related death in the United States. Surgery remains the only potentially curative treatment for pancreatic cancer; however, only 20% of patients present with resectable disease [1]. Even after radical resection, 80% of patients experience recurrence and metastases, as micrometastases have already occurred despite disease being seemingly resectable [2].

Since the hallmark clinical trial in 1997 that showed superiority of gemcitabine (GEM) over 5-fluorouracil, gemcitabine has been the mainstay of treatment of PDAC, either as single agent or in combination with other treatments [1]. Following surgery, adjuvant chemotherapy with gemcitabine was associated with longer progression-free and overall survivals compared to observation alone [3]. For patients with locally advanced and metastatic (LA/M) disease, the 2 main treatment options are FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) [4] and gemcitabine/nab-paclitaxel (n-PC) combination [5], with a progression-free survival (PFS) and overall survival (OS) of 5.5–6.4 months and 8.5–11 months, respectively.

M. Diab · M. S. Hamid
Department of Oncology, Karmanos Cancer Institute, Detroit, MI, USA

R. M. Mohammad
Department of Oncology, Gastrointestinal Cancer Research, Wayne State University School of Medicine, Karmanos Cancer Institute, Detroit, MI, USA

P. A. Philip
Department of Oncology, Department of Pharmacology, Wayne State University School of Medicine, Karmanos Cancer Institute, Hudson-Webber Cancer Research Center, Detroit, MI, USA

A. S. Azmi (✉)
Department of Oncology, Wayne State University School of Medicine, Karmanos Cancer Institute, Detroit, MI, USA
e-mail: azmia@karmanos.org

Nab-paclitaxel (n-PC) is a nanoparticle (130-nm) albumin-bound formulation of paclitaxel; its water solubility gives it the ability to penetrate the tumor microenvironment, leading to an increase in the intratumoral levels of gemcitabine (GEM) [6]. This could be related to inhibition of the GEM-catabolizing enzyme, cytidine deaminase, by n-PC through the production of reactive oxygen species [6]. Combined to GEM, nab-paclitaxel showed improved outcomes in metastatic PDAC; PFS and OS with GEM/n-PC were 5.5 months and 8.5 months, respectively, compared to 3.7 months and 6.7 months with GEM alone, with a response rate of 23%. Grade 3/4 fatigue, neutropenia, peripheral neuropathy, and diarrhea were observed in 17%, 38%, 17%, and 6% of patients, respectively [5]. Most recently, single-agent therapy with the oral fluoropyrimidine derivative S-1 demonstrated non-inferiority to gemcitabine [7].

In the following sections, we will discuss some of the preclinical and clinical advancements in the treatment of PDAC.

Targeting Core Signaling Pathways in Pancreatic Ductal Adenocarcinoma

KRAS and *CDK2NA* represent the most common genetic mutations and are found in more than 90% of cases [8, 9], followed by mutations in *TP53* [10] and *SMAD4* [11], which are observed in 75–85% and 60% of cases, respectively. Mutated KRAS and CDK2NA have been implicated in development of PDAC, while mutations of *TP53* and SMAD4 in its progression [12]. Epigenetic dysregulation also adds to the genomic heterogeneity of PDAC. Even in the absence of inactivating mutations of tumor-suppressor genes, their silencing can occur through methylation [13].

Various efforts were painstakingly undertaken to target major signaling pathways in the biology of PDAC, including the *KRAS* and *EGFR* pathways, as well as targeting the cancer stem cells (CSCs) and tumor stroma. This has been augmented by large cancer sequencing initiatives during the past

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_27

decade that have led to advancements in the comprehension of the molecular mechanisms implicated in the evolution of PDAC [12, 14, 15]. However, despite those laborious efforts, almost all targeted agents failed to show a survival benefit in late clinical trials.

HER1/EGFR Pathway

Epidermal growth factor receptor (EGFR) is a transmembrane receptor member of the ErbB family and is implicated in cell-cycle regulation, cell differentiation, adhesion, and survival. It is overexpressed in 90% of PDAC cases [16]. Its tyrosine kinase domain is activated by a myriad of ligands, including epidermal growth factor (EGF), transformation growth factor α(alpha) (TGF-α), and betacellulin. Through activating EGFR, multiple downstream pathways are activated that eventually conduct its functions. Those pathways include Ras/MAP kinase, phosphatidylinositol 3'-kinase (PI3K)/Akt, Janus kinase/Stat, and phospholipase C/protein kinase C pathways.

The 2 strategies in targeting EGFR are small-molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies. EGFR inhibitors compete with adenosine triphosphate (ATP) for binding to the kinase domain, thereby blocking downstream signaling transduction and preventing the biologic roles of EGFR. Of these agents, erlotinib was the only one to show a very marginal, yet statistically significant, survival benefit. It was approved by the US Food and Drug Administration (FDA) for first-line treatment of chemonaïve patients with locally advanced and metastatic (LA/M) PDAC [17]. However, it is not being used in the clinic at the present time. The phase III trial by Moore et al. enrolled 569 patients with LA/M PDAC who were randomized to receive gemcitabine (GEM) alone or in combination with erlotinib. Patients on the combination therapy arm had a progression-free survival (PFS) and overall survival (OS) of 3.75 and 6.24 months compared to 3.55 and 5.91 months in the GEM arm, respectively [18]. This survival benefit was irrespective of EGFR status [19]. Gefitinib is another inhibitor of EGFR that showed tolerability in phase I/II trials in the setting of previously treated inoperable PDAC in combination with GEM [20]; median PFS and survival of 4.1 months and 7.3 months were observed in a phase II trial in combination with GEM [21].

Cetuximab is a monoclonal antibody (MAB) that binds to the extracellular domain of EGFR that initially showed some promising results in a pilot phase II trial in the setting of LA/M PDAC in combination with GEM [19]. However, no survival benefit was noted in further studies [22–25]. Matuzumab showed tolerability in chemonaïve patients with advanced disease [26], but further evidence on its efficacy is lacking. Nimotuzumab, a humanized MAB, was safe and tolerable when administered as monotherapy for patients with advanced disease who failed prior therapy [27]. When combined with GEM in the setting of first-line treatment for advanced disease, nimotuzumab resulted in response rates of 55.6%, and PFS and OS of 3.71 and 9.29 months, respectively [28]. Nimotuzumab is not currently available in the United States.

HER2 Pathway

Human epidermal growth factor receptor 2 (HER2) is another transmembrane tyrosine kinase receptor member of the ErbB family. It is overexpressed in 11–45% of PDAC cases and has been associated with poorer prognosis [29–31]. Trastuzumab, an MAB, showed some benefit in combination with GEM in preclinical models [29]. In the clinical setting, trastuzumab was tested in combination with GEM [30] as well as capecitabine [32]. The trastuzumab/GEM combination yielded similar results compared to single-agent GEM in metastatic PDAC with overexpression of HER2/neu as evidenced by immunohistochemistry (IHC) [30]. The trastuzumab/capecitabine combination therapy, although proved tolerable in the setting of metastatic PDAC, did not perform favorably in regards to PFS and OS compared to standard chemotherapy [32].

Lapatinib is a reversible, small-molecule TKI that binds to and inhibits both *EGFR* and *HER2* [33]. It was initially approved by the FDA for the treatment of HER2-positive advanced breast cancer in combination with capecitabine [34]. In the setting of PDAC, a phase I trial initially showed promising results in combination with GEM or GEM/oxaliplatin for the treatment of LA/M disease [35]; however, a phase II study of lapatinib/GEM combination therapy failed to show a survival benefit [36]. Most recently, lapatinib was investigated in combination with capecitabine for second-line treatment for GEM-refractory metastatic PDAC, and it showed a PFS and OS of 2.6 and 5.2 months, respectively [37]; no partial responses were observed.

KRAS Pathway and Downstream Signaling Pathways

KRAS is a GTPase protein that belongs to the Ras family and possesses oncogenic activity. The *KRAS* gene is located on chromosome 12p and promotes proliferation and inhibits apoptosis through the downstream pathways RAF/MEK/ERK and PI3K/Akt. *KRAS*-activating mutations are observed in >90% of PDAC cases [8]. Thus far, *KRAS* has been elusive, and no inhibitors exist despite various attempts to establish an effective blocker of its activity [12]. The farnesyl-transferase inhibitor tipifarnib showed some

encouraging results in the preclinical setting [38]. Unfortunately, it did not result in a survival benefit in clinical trials [39]. Therefore, the focus was shifted toward targeting pathways downstream of KRAS.

The RAF/MEK/ERK signaling cascade plays an important role in regulating cell proliferation and differentiation as well as inflammation and survival. It is often deregulated in PDAC due to gain-of-function mutations of the Ras or BRAF oncogenes [40, 41]. Mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) represent central components of this pathway and are appealing targets to inhibit [42–44]. Two oral small-molecule inhibitors of MEK1/2 have been identified. Selumetinib was tested in comparison to capecitabine in the setting of advanced disease [45]. Although the OS in the selumetinib arm was longer than that in the capecitabine arm (5.4 vs. 5.0 months), the difference was not statistically significant [45]. Trametinib was studied in combination with GEM in chemonaïve metastatic PDAC in a phase II randomized, multicenter trial but did not yield any survival benefit [46].

Following its activation, *KRAS* phosphorylates phosphoinositide 3 kinase (PI3K), which in turn activates Akt, a serine/threonine kinase that is overexpressed in PDAC [44, 47]. Similar to the RAF/MEK/ERK pathway, the PI3K/Akt signaling cascade also has important roles in cell proliferation, metabolism, and survival [44], and accomplishes this through downstream signaling targets, including the mammalian target of rapamycin (mTOR). Pharmacological inhibition of PI3K increased the susceptibility of PDAC cell lines to chemotherapy and tumor necrosis factor α(alpha) (TNF-α)-induced apoptosis [48, 49]. Rigosertib is a first-in-class Ras mimetic and small-molecule inhibitor of multiple signaling pathways including polo-like kinase 1 (PLK1) and phosphoinositide 3-kinase (PI3K). It was investigated in combination with GEM for patients with previously untreated, metastatic disease; however, it failed to demonstrate an improvement in survival [50]. Trametinib was also investigated in combination with the pan-PI3K inhibitor buparlisib (BKM120), but the combination therapy failed to show a survival benefit [51]. Enzastaurin, an inhibitor of PI3K/AKT and PKCβ(beta), was studied in combination with GEM in LA/M PDAC but did not show an advantage compared to single-agent GEM [52]. Other trials investigated RX-0201 (an Akt antisense oligonucleotide) in combination with GEM [53], as well as BEZ235 (an inhibitor of PI3K and mTOR) in combination with the MEK inhibitor MEK162 [54], and buparlisib (BMK120) in combination with mFOLFOX-6 [55]; the results have yet to be released.

Inhibiting mTOR was shown to impede the growth of many PDAC cell lines [56] as well as PDAC xenograft growth and metastasis, possibly through induction of endothelial cell death and tumor vessel thrombosis [57]. Single-agent everolimus, an oral mTOR inhibitor, demonstrated minimal to no efficacy in patients with GEM-refractory metastatic PDAC [58, 59]. Combining everolimus with capecitabine was associated with a PFS and OS of 3.6 and 8.9 months, respectively [60]. Temsirolimus, another mTOR inhibitor, in combination with erlotinib also showed discouraging results, and it was hypothesized that the negative feedback loop resulting from the mTOR inhibition might account for the disease progression toxicity observed in the study [59].

Embryonic Pathways

The Hedgehog (HH) and Notch signaling cascade play a crucial role in cell proliferation and in pancreatic organogenesis during embryonic development, and they have been both targeted by novel therapies. The mammalian HH family of secreted signaling proteins includes Sonic, Indian, and Desert HH (SHH, IHH, and DHH, respectively) [61]. Under normal conditions, the HH pathway is negatively regulated by the Patched tumor-suppressor protein, which inactivates the Smoothened protein [61]. When HH ligands bind to the extracellular domain of the Patched protein, they disrupt the inhibition of the Smoothened protein and upregulate the Gli family of transcriptional regulators [62, 63]. Pathological alterations in the HH pathway include loss of the Patched protein, activating mutations of the Smoothened protein, and upregulation of the Hedgehog ligands and Gli proteins [64]. Activation of the HH pathway has been implicated in the evolution and maintenance of PDAC [64, 65], and has been shown to be overexpressed in more than 70% of pancreatic cancers [64]. Specifically, HH-secreted signaling proteins were found to be overexpressed in PDAC stroma and cancer stem cells (CSCs) stromal and CSCs pools, implying an abnormal activation of HH in the main compartment of pancreatic cancer [66] in addition to contributing to the desmoplastic reaction, a crucial feature of pancreatic cancer that limits the delivery of therapeutic agents to pancreatic cancer cells [67]. This has made the HH pathway an active field of research. Two small-molecule inhibitors of Smoothened have been identified so far: vismodegib (GDC-0449) [68] and saridegib (IPI-926) [69]. Vismodegib is being investigated in multiple trials for neoadjuvant therapy [70], as well as in the treatment of LA/M PDAC as single agent (no response [71]) and in combination with GEM [72, 73] (no survival benefit [74]), GEM + nab-paclitaxel [75], GEM + erlotinib [76], and sirolimus [77]. Saridegib is being evaluated in the setting of advanced disease in combination with GEM [78] as well as FOLFIRINOX [79, 80]. Sonidegib (LDE-225), a third Smoothened inhibitor, was evaluated in the setting of other malignancies [81, 82], and is currently under investigation in an ongoing clinical trial for the neoadjuvant treatment of PDAC [83].

The Notch pathway also contributes to tumorigenesis when aberrantly upregulated [84]. Binding of the membrane-bound Notch receptors (Notch 1–4) to their ligands (Delta-like and Jagged) results in proteolysis of the Notch receptor, mediated through γ(gamma)-secretase (presenilin), and the translocation of its activated form, known as the Notch intracellular domain, to the nucleus, where it regulates the transcription of a number of target genes involved in proliferation and differentiation, and interacts with other pathways, including *KRAS* [85]. Notch and its ligands are overexpressed in PDAC [86], and efforts were invested in targeting it. RO4929097 is an oral inhibitor of γ(gamma)-secretase that showed some promising results in a phase II trial in the setting of previously treated metastatic PDAC [87] and has also been studied in combination with GEM [88]. RO4929097 was also investigated in the neoadjuvant setting, but the study was terminated [89]. MK0752, another γ(gamma)-secretase inhibitor, showed tolerability in a phase I trial [90] and was investigated in combination with GEM for the treatment of inoperable disease [91], but more information is required about its efficacy. Demcizumab (OMP-21M18), a humanized immunoglobulin G2 (IgG2) monoclonal antibody targeting the Delta-like ligand 4, was associated with stable disease in a phase I trial [92] and is currently being investigated in 2 ongoing clinical trials for LA/M PDAC [93, 94].

PARP Pathway

The tumor-suppressor *BRCA2* gene is located on chromosome 13q and is inactivated in fewer than 10% of PDAC [95]. Germline mutations in *BRCA2* are associated with a hereditary predisposition to breast, ovarian, and pancreatic cancer [96] via deficiency in DNA damage repair. The poly (ADP-ribose) polymerase (PARP) family is a group of nuclear enzymes that is involved in mechanisms of cell recovery from DNA damage [97]. Under normal conditions, inhibiting PARP members leads to the accumulation of double-strand DNA breaks that are then repaired through the *BRCA*-dependent homologous recombination mechanism [97]. This would make *BRCA1/2*-mutated tumors, at least theoretically, more susceptible to the effects of PARP inhibitors in combination with DNA-damaging therapy. Olaparib is an oral PARP inhibitor that has been investigated in breast and ovarian cancers [98–100]. In advanced GEM-refractory PDAC, single-agent olaparib was associated with a response rate of 21.7% [101]. Trials testing olaparib and veliparib in combination therapy to other treatments, such GEM, are being undertaken [102, 103].

IGFR Pathway

The insulin-like growth factor 1 receptor (IGF1R) and its ligands (insulin-like growth factors 1 and 2) are overexpressed in pancreatic cells [104, 105]. Preclinical studies suggested a protumorigenic role of IGF1R [106]. Upon binding to is ligands, it triggers downstream pathways involved in cell proliferation and survival, such as PIK3/AKT [106]. Its blockade inhibits growth and survival of pancreatic cancer cells, including those that are KRAS-mutated [106].

Its blockade has been evaluated through multiple trials utilizing monoclonal antibodies. Ganitumab initially showed tolerable toxicity in combination with GEM in a phase 2 trial of treatment-naïve metastatic PDAC [107], but the combination failed to improve survival in the hallmark GAMMA trial, and the study was stopped based on results from a preplanned futility analysis [108]. Ganitumab was tested in combination with the death receptor 5 monoclonal antibody agonist conatumumab in the setting of LA/M PDAC [109]. Death receptor 5 is a member of the TRAIL receptor family, and its activation leads to apoptosis [110]. Unfortunately, although the combination therapy was tolerable, it did not yield objective responses [109]. Dual blockade of EGFR and IGF1R signaling through combining cixutumumab, another IGF1R monoclonal antibody antagonist, with erlotinib and GEM failed to show a survival benefit in untreated metastatic disease [111].

Wnt-β(beta)-Catenin Pathway

The Wnt-β(beta)-catenin pathway plays a central role in pancreatic cancer progression and cancer stem cells maintenance [112]. PRI-724 is a cyclic AMP-response element binding protein/β(beta)-catenin modulator that induces stem cell differentiation [113]. It is currently being investigated in combination with GEM in the treatment of metastatic disease [114].

Inhibition of Angiogenesis

Vascular endothelial growth factor (VEGF) plays a key role in neoangiogenesis, a crucial mechanism for tumor growth and metastasis [115], and is overexpressed in PDAC [116]. Bevacizumab (BV) is a monoclonal antibody against VEGF that was associated with improved survival in metastatic colorectal cancer [117], and many trials evaluated its efficacy in PDAC, but most failed to show a survival benefit. Despite initial promising results with the BV/GEM combination in the setting of metastatic PDAC [118], a phase III trial failed to show a survival benefit with this combination

[119]. Furthermore, no survival benefit was observed from erlotinib/BV [120] and GEM/erlotinib/BV [121] combination in the setting of metastatic disease. A phase II trial investigating cetuximab plus BV with or without GEM was terminated early due to lack of sufficient efficacy in both treatment arms [122]. Following encouraging results with chemotherapy doublets (GEM plus capecitabine) in combination with biologic doublet (BV plus erlotinib) [123], a phase I/II trial showed median PFS and OS of 8.4 and 12.6 months, respectively, with a confirmed radiological response rate of 23% [124]. The combination of BV with PARP inhibitor olaparib was well tolerated in a phase I trial, but more evidence is lacking on its efficacy [125].

Axitinib is another potent, selective inhibitor of VEGF receptors 1, 2, and 3. Adding axitinib to GEM in LA/M PDAC did not improve survival [126]. Similarly, sorafenib, a multikinase inhibitor of B-raf, VEGF receptor 2, and platelet-derived growth factor (PDGF) receptor β(beta), was not associated with a survival benefit in combination with GEM in advanced PDAC [127]. Aflibercept is a fully humanized recombinant fusion protein composed of portions of the extracellular domains of VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G1 [128]. It binds to VEGF-A, VEGF-B, as well as placental growth factors 1 and 2 (PlGF)-1 and PlGF-2 and thus prevents those ligands from binding to VEGF receptor [128]. It was shown to suppress tumor growth in preclinical models [128]; however, a phase III trial evaluating aflibercept in combination with GEM as first-line therapy for metastatic PDAC was terminated due to futility following a planned interim analysis [129]. Vatalanib is an oral poly-tyrosine kinase inhibitor with strong affinity for PDGF and VEGF receptors. It was tested as single-agent therapy in GEM-refractory LA/M PDAC and was associated with a 6-month survival rate of 29% [130].

Other trials investigated the role of non-steroidal anti-inflammatory medications, such as celecoxib and TL-118. Combining celecoxib with GEM in LA/M PDAC did not demonstrate significant improvement in measured clinical outcomes; 4 of the 25 enrolled patients had a partial response and 7 had stable disease [131]. The trial investigating TL-118 in combination with GEM is still ongoing [132].

Targeting the Tumor Stroma

The tumor stroma has recently emerged as one of the crucial players in the resistance of PDAC to chemotherapy, after it was initially thought to be a mechanical barrier to protect the host [133]. Formed as a result of a desmoplastic reaction, the stroma forms the bulk of the tumoral structure, accounting for up to 90% of the tumor anatomy, and is comprised of pancreatic stellate cells/tumor-associated fibroblasts, endothelial cells, immune cells, and tumor cells, in addition to extracellular matrix (ECM) proteins and growth factors [134]. Pancreatic stellate cells/tumor-associated fibroblasts remain quiescent until their activation by various cytokines, growth factors, and oxidative stress, following which they transform into myofibroblast-like cells and secrete large amounts of extracellular matrix (ECM) proteins and growth factors, all of which nurture the proliferation of pancreatic cancer cells [133]. Additionally, this accumulation of ECM proteins increases the interstitial pressure, causing compression of the capillaries and the subsequent impaired blood perfusion, which in part decreases drug delivery and in part induces a hypoxic state that further promotes tumor survival and invasion through activation of a range of genes by hypoxia-inducible factor 1-α(alpha) and inducing epithelial-mesenchymal transition (EMT) [135].

Due to the versatile roles that pancreatic stellate cells play in the survival and chemoresistance of pancreatic cells, they have been the target of some therapeutic agents. Dovitinib (TKI258) is a small-molecule, potent multikinase inhibitor of VEGF1, 2, and 3, fibroblast growth factor receptors 1, 2, and 3 (FGFR), and platelet-derived growth factor receptor β(beta) (PDGFR) that are expressed on pancreatic stellate cells [136]. It was evaluated in phase I studies for the treatment of various solid tumors [136, 137] and has been investigated in the treatment of advanced/metastatic PDAC in combination with GEM and capecitabine [138]. Another cell type that was linked to poor prognosis in PDAC is mast cells; masitinib, a selective c-Kit inhibitor that efficiently inhibits mast cell function, has been under investigation in a phase III trial in combination with GEM for LA/M disease [139].

Targeting the stromal connective tissue has also been attempted. Although the use of matrix metalloproteinase inhibitors showed no additional benefit compared to single-agent GEM or in combination to GEM [140, 141], PEGPH20, a pegylated formation of recombinant hyaluronidase, was associated with a survival benefit in combination with GEM especially in hyaluronan-rich tumors [142]. It has been under investigation in multiple ongoing trials in the setting of metastatic disease [143–145].

Utilizing Delivery Systems

The liposomal delivery system is comprised of phospholipid-based vesicles containing the inhibitor payload conjugated to a specific carrier that actively targets surface receptors, leading to engagement and subsequent internalization via endocytic pathway and subsequent release into the cytosol due to low pH exposure. Multiple inhibitors can be delivered in this manner that can exhibit their cellular effects by improving their cellular concentration in the specific targeted cells.

Liposomal delivery of geranylgeranyltransferase inhibitors (GGTI) and farnesyltransferase inhibitors (FTI) leads to synergistic inhibition of membrane signaling proteins and K-Ras signaling in MiaPaCa-2 cell line, whereas freeform combinations resulted in greater cytotoxic effects [146]. The same group was successful in targeting transferrin receptors that are overexpressed in cancer cells. Sequencing with another nanoparticle in a stepwise manner can further enhance drug delivery by helping overcoming resistance induced by desmoplastic stromal reaction. In a novel approach, a first-wave liposome was introduced containing LY364947, a selective TGF-β(beta) type-I receptor, which disrupted the molecular cascade responsible for pericyte cell differentiation, endothelial cell coverage, and blood vessel stabilization, resulting in improved vascular access through open vascular fenestrations. This technique increased the gemcitabine availability to be delivered by the second-wave liposome [147]. Pegylated-modified liposomes can improve the pharmacokinetics further by improving drug circulation time. Alternatively, combining the payload with an amphipathic molecule containing both an inner, non-polar, hydrophobic region, and an exterior-facing, polar, hydrophilic region can increase the solubility of non-efficacious inhibitors. In an in vivo study involving subcutaneous tumor in athymic nude mice, vismodegib, a hydrophobic Smoothened (SMO) cell surface receptor antagonist, was encapsulated with a copolymer micelle that was complexed with the highly soluble oligonucleotide K-RAS inhibitor miR-let7b. The combination allowed for longer mean residence time of miR-let7b and similar biodistribution in implanted ectopic MIA PaCa-2 cells [148]. In another in vivo study, encapsulating PH-427, a AKT/PDK1 inhibitor, into a poly(lactic-co-glycolic acid) (PLGA) biodegradable polymer to form PH-427-PNP complex improved drug delivery by concealing the hydrophobicity of PH-427 and allowing for intravenous delivery of the inhibitor [149]. As drug-loaded PLGA molecule exhibits a biphasic release pattern, with an initial burst release of loosely bound surface payload followed by a slower dissipation phase [150], further modification to the nanoparticle by supplementing the polymer with an additional layer has been shown to have a more delayed and sustained drug release in an in vivo study involving PH-427-PNP complexes [151]. Nanoparticles can be engineered to deliver agents at considerably lower dose with the aim of decreasing drug interruption and cessation. In a novel combined approach, photodynamic therapy was first utilized to irradiate the tumor site containing AsPC1 cells and subsequently followed by delivery of photosensitive benzoporphyrin-linked nanoliposome and containing cabozantinib, a tyrosine kinase inhibitor targeting VEGFR and MET signaling. This photorelease of the inhibitor augmented the antivascular effect of PDT while also prevented metastatic escape via the MET pathway [152].

Micro Ribonucleic Acids

MicroRNAs (miRNA) are small (19–25 nucleotides) non-coding ribonucleic acids (RNAs) that interact with messenger RNA (mRNA) and serve as negative regulators of gene expression [153, 154] by binding to imperfect complementary regions in the 3' untranslated region of the target messenger RNA (mRNAs), inhibiting their translation or leading to their degradation. They have been shown to influence cell differentiation, proliferation, and apoptosis [155]. They represent only 3% of the human genome but regulate 20–30% of the protein coding genes [156, 157]. They have been profiled in many different malignancies including breast [158], lung [159], and colorectal cancer [160], and differential expression was detected with those malignancies, all of which has made miRNAs promising biomarkers in the screening, diagnosis, treatment, and prognosis of PDAC. miRNA-96, -126, and -217, all of which target *KRAS*, were found to be downregulated in PDAC compared to other noncancerous as well as normal pancreatic tissue [161–163]. Furthermore, reexpression of miR-96 and 217 suppressed *KRAS* activity and resulted in reduced tumor migration and invasion, suggesting their role as tumor suppressors [162, 163]. Several miRNA profiles were observed to discriminate PC from benign pancreatic pathology and healthy samples. Circulating miRNA-483-3p levels are overexpressed in PDAC compared to intrapapillary mucinous neoplasms and healthy controls [164]. Elevated serum miR-200a and -200b levels were associated with silencing of SIP1 and overexpression of E-cadherin in patients with pancreatic cancer and chronic pancreatitis compared to healthy controls [165]. As miRNAs regulate multiple gene expressions and signaling pathways, miRNA-based therapies are at an advantage over single-gene therapy, and, at least hypothetically, targeting miRNAs is expected to produce more effective anticancer activities. Transfecting pancreatic CSCs with an miR-200c mimic decreased colony formation, invasion, and chemoresistance of pancreatic CSCs by regulating EMT [166]. Lu et al. reached similar results with transfection of miR-200a [167]. On the same note, transfecting gemcitabine-resistant pancreatic cells with miRNA-205 and miR-7 reduced the expression of TUBB3 and Pak-1, respectively, and reduced the CSC population [168]. Despite their significant role in disease biology, the miRNAs are yet to be incorporated in therapeutic clinical trials for PDAC. To date there are few observational clinical studies that are looking into the role of miRNAs in PDAC diagnosis in comparison to more routine tests such as fluorescence in situ hybridization (FISH) and CA 19–9 (ClinicalTrials.gov Identifier: NCT02531607).

Other Notable Therapies in Pancreatic Ductal Adenocarcinoma

Liposomal Irinotecan

PEP02 (also known as MM-398) is a nanoparticle liposomal irinotecan that provides enhanced bio-distribution and superior pharmacokinetics compared to traditional irinotecan [169]. PEP02 has been studied as single agent as well as in combination therapy in advanced, GEM-refractory PDAC. In 40 enrolled patients, single-agent PEP02 was associated with a PFS and OS of 2.4 and 5.2 months, respectively. In the phase 3 NAPOLI-1 trial, 417 patients with metastatic PDAC previously treated with a GEM-based regimen were randomized to single-agent PEP02, PEP02 with 5-fluorouracil (5-FU)/leucovorin, or 5-FU/leucovorin alone [170]. OS was superior in the PEP02+5-FU/leucovorin arm compared to the 5-FU/leucovorin arm (6.1 vs. 4.2 months, $p = 0.012$), and no difference in OS was noted between the PEP02 and the 5-FU/leucovorin arms. The NAPOLI-1 trial did not compare traditional irinotecan to PEP02.

TH-302

TH-302 is a hypoxia-activated pro-drug that releases the DNA alkylator bromo-isophosphoramide mustard in hypoxic settings. The TH-302/GEM combination was investigated as a first-line treatment of LA/M PDAC [171]. In 214 patients randomized to either single-agent GEM, GEM with TH-302 at a dose of 240 mg/m^2 (G+T240), or GEM with TH-302 at a dose of 340 mg/m^2 (G+T340), PFS was longer with combination therapy compared to single-agent GEM (5.6 vs. 3.6 months, $p = 0.005$). PFS rates for G+T240 and G+T340 were 5.6 and 6.0 months, respectively. Median OS times for gemcitabine, G+T240, and G+T340 were 6.9, 8.7, and 9.2 months, respectively, but the results were not statistically significant.

Novel Regimens in the Pipeline for Pancreatic Ductal Adenocarcinoma

Nucleo-cytoplasmic transport is a fundamental process in normal and abnormal tissues alike, and its dysregulation has been elucidated in a number of hematological and solid malignancies [172]. Cancer cells exploit these processes to stimulate tumor growth and to effectively evade apoptotic mechanisms [172]. Exportin 1 (XPO1) (also known as chromosome region maintenance 1 [CRM1]) represents the main mediator of nuclear export in many cell types and mediates cell proliferation through a number of pathways [173]. XPO1 interacts with nucleoporins (NUP214 and NUP88) in the nuclear pore complex [173] and transports cargo proteins containing nuclear export signals (NES) out of the cell nucleus [174]. NES are short leucine-rich sequences that can be found in many shuttling proteins, including numerous tumor suppressors and oncogenes [174]. Nuclear proteins exported into the cytoplasm by XPO1 in cancer cells include the drug targets [175, 176], such as topoisomerase IIα(alpha), and tumor-suppressor proteins [177–181], such as p53, Rb, and APC. This has made nuclear export a potential target for therapeutic intervention in cancer by small-molecule nuclear export inhibitors [182]. Selinexor, a selective inhibitor of nuclear export, initially known as KPT-330, showed safety and tolerability in a phase I trial of 189 patients that included 11 patients with pancreatic cancer [183]. Grade 3/4 adverse effects included toxicities were thrombocytopenia (16%), fatigue (15%), and hyponatremia (13%) [183]. Selinexor is currently being investigated in a phase Ib/II trial in combination with GEM and n-PC for the treatment of patients with metastatic PDAC [184].

Conclusion

Despite the many efforts in treating PDAC, it remains the fourth leading cause of cancer-related deaths. Its chemoresistance stems from key features, including its genomic heterogeneity, its dense stroma, and its cancer stem cells which play a crucial role in its survival. The mainstay therapy for advanced disease is GEM + nab-paclitaxel or FOLFIRINOX for patients with a good performance status. Although the past decade unraveled new molecular pathways that feed the development and survival of PDAC, most efforts to identify target therapy have failed to show a survival benefit (Table 27.1 and Table 27.2 [4, 5, 18]). The exception is the combination erlotinib/GEM, which showed a modest, yet statistically significant, survival benefit. Targeting *KRAS*, which is mutated in more than 90% of PDAC, has been unsuccessful, and the focus was shifted to target downstream pathways instead. Targeting multiple

Table 27.1 Landmark positive trials for locally advanced and metastatic pancreatic ductal adenocarcinoma

Treatment	Control	Number of patients	Response rate (%)	PFS (months)	OS (months)	Reference
FOLFIRINOX	GEM	342	32 vs. 9.4	6.4 vs. 3.3	11.1 vs. 6.8	[4]
Nab-paclitaxel + GEM	GEM	861	23 vs. 7	5.5 vs. 3.7	8.5 vs. 6.7	[5]
Erlotinib + GEM	GEM	569	8.6 vs. 8	3.75 vs. 3.55	6.24 vs. 5.91	[18]

PFS progression-free survival, *OS* overall survival, *FOLFIRINOX* folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin, *GEM* gemcitabine

Table 27.2 Ongoing trials

Trial identifier	Agent	Target
NCT01728818	Afatinib	EGFR, HER2, HER4
NCT01571024	BKM120	PI3K/Akt and mTOR
NCT01028495	RX-0201	PI3K/Akt and mTOR
NCT01337765	BEZ235 + MEK162	PI3K/Akt, mTOR, and MEK
NCT01096732	GDC-0449	Hedgehog pathway
NCT01195415	GDC-0449 + GEM	Hedgehog pathway
NCT00878163	GDC-0449 + erlotinib	Hedgehog pathway
NCT01431794	LDE-225	Hedgehog pathway
NCT01576666	LDE225	Hedgehog pathway
NCT00515866	KU-0059436	PARP Pathway
NCT01296763	AZD2281	PARP Pathway
NCT01764477	PRI-724	Wnt-β-catenin pathway
NCT01621243	Necuparanib	Angiogenesis
NCT01509911	TL-118	Angiogenesis
NCT01497392	Dovitinib	Tumor stroma
NCT00789633	Masitinib	Tumor stroma
NCT01453153	PEGPH20 + GEM	Tumor stroma
NCT01839487	PEGPH20 + nab-paclitaxel + GEM	Tumor stroma
NCT02241187	PEGPH20 + cetuximab	Tumor stroma

core signaling pathways might also be a more feasible approach to achieve more encouraging results. Innovative methods of targeting the various pathways that block the malicious nature of this disease remain in dire need.

References

1. Rosewicz S, Wiedenmann B. Pancreatic carcinoma. Lancet. 1997;349(9050):485–9.
2. O'Reilly EM. Refinement of adjuvant therapy for pancreatic cancer. JAMA. 2010;304(10):1124–5.
3. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.
4. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
5. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
6. Frese KK, Neesse A, Cook N, Bapiro TE, Lolkema MP, Jodrell DI, et al. nab-Paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. Cancer Discov. 2012;2(3):260–9.
7. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol. 2013;31(13):1640–8.
8. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell. 1988;53(4):549–54.
9. Caldas C, Hahn SA, da Costa LT, Redston MS, Schutte M, Seymour AB, et al. Frequent somatic mutations and homozygous deletions of the p16 (MTS1) gene in pancreatic adenocarcinoma. Nat Genet. 1994;8(1):27–32.
10. Redston MS, Caldas C, Seymour AB, Hruban RH, da Costa L. Yeo CJ, et al. p53 mutations in pancreatic carcinoma and evidence of common involvement of homocopolymer tracts in DNA microdeletions. Cancer Res. 1994;54(11):3025–33.
11. Hahn SA, Schutte M, Hoque AT, Moskaluk CA, da Costa LT, Rozenblum E, et al. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science. 1996;271(5247):350–3.
12. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321(5897):1801–6.
13. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791):607–20.
14. Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. 2012;491(7424):399–405.
15. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
16. Xiong HQ, Abbruzzese JL. Epidermal growth factor receptor-targeted therapy for pancreatic cancer. Semin Oncol. 2002;29(5 Suppl 14):31–7.
17. Senderowicz AM, Johnson JR, Sridhara R, Zimmerman P, Justice R, Pazdur R. Erlotinib/gemcitabine for first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas. Oncology (Williston Park). 2007;21(14):1696–706; discussion 706-9, 712, 715.
18. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960–6.
19. da Cunha Santos G, Dhani N, Tu D, Chin K, Ludkovski O, Kamel-Reid S, et al. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA.3. Cancer. 2010;116(24):5599–607.
20. Carneiro BA, Brand RE, Fine E, Knop RH, Khandekar JD, Uhlig W, et al. Phase I trial of fixed dose rate infusion gemcitabine with gefitinib in patients with pancreatic carcinoma. Cancer Investig. 2007;25(5):366–71.
21. Fountzilas G, Bobos M, Kalogera-Fountzila A, Xiros N, Murray S, Linardou H, et al. Gemcitabine combined with gefitinib in patients with inoperable or metastatic pancreatic cancer: a phase II Study of the Hellenic Cooperative Oncology Group with biomarker evaluation. Cancer Investig. 2008;26(8):784–93.
22. Cascinu S, Berardi R, Labianca R, Siena S, Falcone A, Aitini E, et al. Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial. Lancet Oncol. 2008;9(1):39–44.
23. Kullmann F, Hollerbach S, Dollinger MM, Harder J, Fuchs M, Messmann H, et al. Cetuximab plus gemcitabine/oxaliplatin (GEMOXCET) in first-line metastatic pancreatic cancer: a multicentre phase II study. Br J Cancer. 2009;100(7):1032–6.
24. Philip PA, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol. 2010;28(22):3605–10.
25. Fensterer H, Schade-Brittinger C, Muller HH, Tebbe S, Fass J, Lindig U, et al. Multicenter phase II trial to investigate safety and efficacy of gemcitabine combined with cetuximab

as adjuvant therapy in pancreatic cancer (ATIP). Ann Oncol. 2013;24(10):2576–81.
26. Graeven U, Kremer B, Sudhoff T, Killing B, Rojo F, Weber D, et al. Phase I study of the humanised anti-EGFR monoclonal antibody matuzumab (EMD 72000) combined with gemcitabine in advanced pancreatic cancer. Br J Cancer. 2006;94(9):1293–9.
27. Strumberg D, Schultheis B, Scheulen ME, Hilger RA, Krauss J, Marschner N, et al. Phase II study of nimotuzumab, a humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody, in patients with locally advanced or metastatic pancreatic cancer. Investig New Drugs. 2012;30(3):1138–43.
28. Su D, Jiao SC, Wang LJ, Shi WW, Long YY, Li J, et al. Efficacy of nimotuzumab plus gemcitabine usage as first-line treatment in patients with advanced pancreatic cancer. Tumour Biol. 2014;35(3):2313–8.
29. Kimura K, Sawada T, Komatsu M, Inoue M, Muguruma K, Nishihara T, et al. Antitumor effect of trastuzumab for pancreatic cancer with high HER-2 expression and enhancement of effect by combined therapy with gemcitabine. Clin Cancer Res. 2006;12(16):4925–32.
30. Safran H, Iannitti D, Ramanathan R, Schwartz JD, Steinhoff M, Nauman C, et al. Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress HER-2/neu. Cancer Investig. 2004;22(5):706–12.
31. Yamanaka Y, Friess H, Kobrin MS, Buchler M, Kunz J, Beger HG, et al. Overexpression of HER2/neu oncogene in human pancreatic carcinoma. Hum Pathol. 1993;24(10):1127–34.
32. Harder J, Ihorst G, Heinemann V, Hofheinz R, Moehler M, Buechler P, et al. Multicentre phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer. Br J Cancer. 2012;106(6):1033–8.
33. Xia W, Mullin RJ, Keith BR, Liu LH, Ma H, Rusnak DW, et al. Anti-tumor activity of GW572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways. Oncogene. 2002;21(41):6255–63.
34. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355(26):2733–43.
35. Safran H, Miner T, Resnick M, Dipetrillo T, McNulty B, Evans D, et al. Lapatinib/gemcitabine and lapatinib/gemcitabine/oxaliplatin: a phase I study for advanced pancreaticobiliary cancer. Am J Clin Oncol. 2008;31(2):140–4.
36. Safran H, Miner T, Bahary N, Whiting S, Lopez CD, Sun W, et al. Lapatinib and gemcitabine for metastatic pancreatic cancer. A phase II study. Am J Clin Oncol. 2011;34(1):50–2.
37. Wu Z, Gabrielson A, Hwang JJ, Pishvaian MJ, Weiner LM, Zhuang T, et al. Phase II study of lapatinib and capecitabine in second-line treatment for metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2015;76(6):1309–14.
38. End DW, Smets G, Todd AV, Applegate TL, Fuery CJ, Angibaud P, et al. Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. Cancer Res. 2001;61(1):131–7.
39. Van Cutsem E, van de Velde H, Karasek P, Oettle H, Vervenne WL, Szawlowski A, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol. 2004;22(8):1430–8.
40. Wang D, Boerner SA, Winkler JD, LoRusso PM. Clinical experience of MEK inhibitors in cancer therapy. Biochim Biophys Acta. 2007;1773(8):1248–55.
41. Messersmith WA, Hidalgo M, Carducci M, Eckhardt SG. Novel targets in solid tumors: MEK inhibitors. Clin Adv Hematol Oncol. 2006;4(11):831–6.
42. Baccarini M. Second nature: biological functions of the Raf-1 "kinase". FEBS Lett. 2005;579(15):3271–7.
43. Hirano T, Shino Y, Saito T, Komoda F, Okutomi Y, Takeda A, et al. Dominant negative MEKK1 inhibits survival of pancreatic cancer cells. Oncogene. 2002;21(38):5923–8.
44. Gysin S, Lee SH, Dean NM, McMahon M. Pharmacologic inhibition of RAF-->MEK-->ERK signaling elicits pancreatic cancer cell cycle arrest through induced expression of p27Kip1. Cancer Res. 2005;65(11):4870–80.
45. Bodoky G, Timcheva C, Spigel DR, La Stella PJ, Ciuleanu TE, Pover G, et al. A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy. Investig New Drugs. 2012;30(3):1216–23.
46. Infante JR, Papadopoulos KP, Bendell JC, Patnaik A, Burris HA 3rd, Rasco D, et al. A phase 1b study of trametinib, an oral Mitogen-activated protein kinase kinase (MEK) inhibitor, in combination with gemcitabine in advanced solid tumours. Eur J Cancer. 2013;49(9):2077–85.
47. Cheng JQ, Ruggeri B, Klein WM, Sonoda G, Altomare DA, Watson DK, et al. Amplification of AKT2 in human pancreatic cells and inhibition of AKT2 expression and tumorigenicity by antisense RNA. Proc Natl Acad Sci U S A. 1996;93(8):3636–41.
48. Ng SSW, Tsao MS, Chow S, Hedley DW. Inhibition of phosphatidylinositide 3-kinase enhances gemcitabine-induced apoptosis in human pancreatic cancer cells. Cancer Res. 2000;60(19):5451–5.
49. Perugini RA, McDade TP, Vittimberga FJ Jr, Callery MP. Pancreatic cancer cell proliferation is phosphatidylinositol 3-kinase dependent. J Surg Res. 2000;90(1):39–44.
50. O'Neil BH, Scott AJ, Ma WW, Cohen SJ, Leichman L, Aisner DL, et al. A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer. Ann Oncol. 2015;26(12):2505.
51. Bedard PL, Tabernero J, Janku F, Wainberg ZA, Paz-Ares L, Vansteenkiste J, et al. A phase Ib dose-escalation study of the oral pan-PI3K inhibitor buparlisib (BKM120) in combination with the oral MEK1/2 inhibitor trametinib (GSK1120212) in patients with selected advanced solid tumors. Clin Cancer Res. 2015;21(4):730–8.
52. Richards DA, Kuefler PR, Becerra C, Wilfong LS, Gersh RH, Boehm KA, et al. Gemcitabine plus enzastaurin or single-agent gemcitabine in locally advanced or metastatic pancreatic cancer: results of a phase II, randomized, noncomparative study. Investig New Drugs. 2011;29(1):144–53.
53. Rexahn Pharmaceuticals Inc. A safety and efficacy study of RX-0201 Plus Gemcitabine in metastatic pancreatic cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01028495.
54. Array BioPharma. Safety, Pharmacokinetics and Pharmacodynamics of BEZ235 Plus MEK162 in Selected Advanced Solid Tumor Patients. In: Clinicaltrialsgov. Available at: https://clinicaltrials.gov/ct2/show/NCT01337765.
55. UNC Lineberger Comprehensive Cancer Center. BKM120 + mFOLFOX6 in Advanced Solid Tumors With Expansion Cohort Pancreatic Cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01571024.
56. Asano T, Yao Y, Zhu J, Li D, Abbruzzese JL, Reddy SA. The rapamycin analog CCI-779 is a potent inhibitor of pancreatic cancer cell proliferation. Biochem Biophys Res Commun. 2005;331(1):295–302.
57. Bruns CJ, Koehl GE, Guba M, Yezhelyev M, Steinbauer M, Seeliger H, et al. Rapamycin-induced endothelial cell death and tumor vessel thrombosis potentiate cytotoxic therapy against pancreatic cancer. Clin Cancer Res. 2004;10(6):2109–19.
58. Wolpin BM, Hezel AF, Abrams T, Blaszkowsky LS, Meyerhardt JA, Chan JA, et al. Oral mTOR inhibitor everolimus in patients

with gemcitabine-refractory metastatic pancreatic cancer. J Clin Oncol. 2009;27(2):193–8.
59. Javle MM, Shroff RT, Xiong H, Varadhachary GA, Fogelman D, Reddy SA, et al. Inhibition of the mammalian target of rapamycin (mTOR) in advanced pancreatic cancer: results of two phase II studies. BMC Cancer. 2010;10:368.
60. Kordes S, Klumpen HJ, Weterman MJ, Schellens JH, Richel DJ, Wilmink JW. Phase II study of capecitabine and the oral mTOR inhibitor everolimus in patients with advanced pancreatic cancer. Cancer Chemother Pharmacol. 2015;75(6):1135–41.
61. Ingham PW, McMahon AP. Hedgehog signaling in animal development: paradigms and principles. Genes Dev. 2001;15(23):3059–87.
62. Pasca di Magliano M, Hebrok M. Hedgehog signalling in cancer formation and maintenance. Nat Rev Cancer. 2003;3(12):903–11.
63. Taipale J, Beachy PA. The Hedgehog and Wnt signalling pathways in cancer. Nature. 2001;411(6835):349–54.
64. Thayer SP, di Magliano MP, Heiser PW, Nielsen CM, Roberts DJ, Lauwers GY, et al. Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis. Nature. 2003;425(6960):851–6.
65. Berman DM, Karhadkar SS, Maitra A, Montes De Oca R, Gerstenblith MR, Briggs K, et al. Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumours. Nature. 2003;425(6960):846–51.
66. Di Marco M, Macchini M, Vecchiarelli S, Sina S, Biasco G. Hedgehog signaling: from the cuirass to the heart of pancreatic cancer. Pancreatology. 2012;12(4):388–93.
67. Bailey JM, Swanson BJ, Hamada T, Eggers JP, Singh PK, Caffery T, et al. Sonic hedgehog promotes desmoplasia in pancreatic cancer. Clin Cancer Res. 2008;14(19):5995–6004.
68. Singh BN, Fu J, Srivastava RK, Shankar S. Hedgehog signaling antagonist GDC-0449 (Vismodegib) inhibits pancreatic cancer stem cell characteristics: molecular mechanisms. PLoS One. 2011;6(11):e27306.
69. Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science. 2009;324(5933):1457–61.
70. Van Laethem JL. Effect on tumor perfusion of a chemotherapy combining Gemcitabine and Vismodegib before surgery in pancreatic cancer (NEOPACHI-001). In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01713218.
71. LoRusso PM, Rudin CM, Reddy JC, Tibes R, Weiss GJ, Borad MJ, et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. Clin Cancer Res. 2011;17(8):2502–11.
72. National Cancer Institute (NCI). Vismodegib and Gemcitabine Hydrochloride in Treating Patients With Advanced Pancreatic Cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01195415.
73. National Cancer Institute (NCI). Gemcitabine Hydrochloride With or Without Vismodegib in Treating Patients With Recurrent or Metastatic Pancreatic Cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01064622.
74. Catenacci DV, Junttila MR, Karrison T, Bahary N, Horiba MN, Nattam SR, et al. Randomized phase Ib/II study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. J Clin Oncol. 2015;33(36):4284–92.
75. Sidney Kimmel Comprehensive Cancer Center. Hedgehog inhibitors for metastatic adenocarcinoma of the pancreas. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01088815.
76. National Cancer Institute (NCI). GDC-0449 and Erlotinib hydrochloride with or without Gemcitabine Hydrochloride in treating patients with metastatic pancreatic cancer or solid tumors that cannot be removed by surgery. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT00878163.
77. Mayo Clinic. Sirolimus and Vismodegib in Treating Patients With Solid Tumors or Pancreatic Cancer That is Metastatic or Cannot Be Removed By Surgery. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01537107.
78. Infinity Pharmaceuticals Inc. A Study Evaluating IPI-926 in Combination With Gemcitabine in Patients With Metastatic Pancreatic Cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01130142.
79. Andrew Ko. FOLFIRINOX Plus IPI-926 for Advanced Pancreatic Adenocarcinoma. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01383538.
80. Ko AH, LoConte N, Tempero MA, Walker EJ, Kate Kelley R, Lewis S, et al. A phase I study of FOLFIRINOX Plus IPI-926, a Hedgehog pathway inhibitor, for advanced pancreatic adenocarcinoma. Pancreas. 2016;45(3):370–5.
81. Zhou J, Quinlan M, Hurh E, Sellami D. Exposure-response analysis of Sonidegib (LDE225), an oral inhibitor of the Hedgehog signaling pathway, for effectiveness and safety in patients with advanced solid tumors. J Clin Pharmacol. 2016;20.
82. Irvine DA, Zhang B, Kinstrie R, Tarafdar A, Morrison H, Campbell VL, et al. Deregulated hedgehog pathway signaling is inhibited by the smoothened antagonist LDE225 (Sonidegib) in chronic phase chronic myeloid leukaemia. Sci Rep. 2016;6:25476.
83. Sidney Kimmel Comprehensive Cancer Center. Gemcitabine + Nab-paclitaxel With LDE-225 (Hedgehog Inhibitor) as Neoadjuvant therapy for pancreatic adenocarcinoma. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01431794.
84. Radtke F, Raj K. The role of Notch in tumorigenesis: oncogene or tumour suppressor? Nat Rev Cancer. 2003;3(10):756–67.
85. Sundaram MV. The love-hate relationship between Ras and Notch. Genes Dev. 2005;19(16):1825–39.
86. Miyamoto Y, Maitra A, Ghosh B, Zechner U, Argani P, Iacobuzio-Donahue CA, et al. Notch mediates TGF alpha-induced changes in epithelial differentiation during pancreatic tumorigenesis. Cancer Cell. 2003;3(6):565–76.
87. De Jesus-Acosta A, Laheru D, Maitra A, Arcaroli J, Rudek MA, Dasari A, et al. A phase II study of the gamma secretase inhibitor RO4929097 in patients with previously treated metastatic pancreatic adenocarcinoma. Investig New Drugs. 2014;32(4):739–45.
88. National Cancer Institute (NCI). Gamma-Secretase Inhibitor RO4929097 and Gemcitabine hydrochloride in treating patients with advanced solid tumors. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01145456.
89. National Cancer Institute (NCI). RO4929097 Before surgery in treating patients with pancreatic cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01192763.
90. Krop I, Demuth T, Guthrie T, Wen PY, Mason WP, Chinnaiyan P, et al. Phase I pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with advanced solid tumors. J Clin Oncol. 2012;30(19):2307–13.
91. Cancer Research UK. MK0752 and Gemcitabine hydrochloride in treating patients with stage III and IV pancreatic cancer that cannot be removed by surgery. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01098344.
92. Smith DC, Eisenberg PD, Manikhas G, Chugh R, Gubens MA, Stagg RJ, et al. A phase I dose escalation and expansion study of the anticancer stem cell agent demcizumab (anti-DLL4) in patients with previously treated solid tumors. Clin Cancer Res. 2014;20(24):6295–303.
93. OncoMed Pharmaceuticals Inc. Study of Gemcitabine, Abraxane® Plus Placebo Versus Gemcitabine, Abraxane® Plus 1 or 2 truncated courses of Demcizumab in subjects with 1st-line

metastatic pancreatic ductal Adenocarcinoma (YOSEMITE). In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT02289898.
94. OncoMed Pharmaceuticals Inc. A Study of Gemcitabine and Demcizumab (OMP-21M18) with or without Abraxane® as 1st-line treatment in subjects with locally advanced or metastatic pancreatic cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01189929.
95. Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996;56(23):5360–4.
96. Lal G, Liu G, Schmocker B, Kaurah P, Ozcelik H, Narod SA, et al. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. Cancer Res. 2000;60(2):409–16.
97. Tentori L, Graziani G. Chemopotentiation by PARP inhibitors in cancer therapy. Pharmacol Res. 2005;52(1):25–33.
98. Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet. 2010;376(9737):245–51.
99. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376(9737):235–44.
100. Fong PC, Yap TA, Boss DS, Carden CP, Mergui-Roelvink M, Gourley C, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol. 2010;28(15):2512–9.
101. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244–50.
102. Gemcitabine Hydrochloride and Cisplatin with or without Veliparib or Veliparib alone in treating patients with locally advanced or metastatic pancreatic cancer [database on the Internet]. Available from https://clinicaltrials.gov/ct2/show/NCT01585805. Identifier NCT01585805.
103. Study to assess the safety & tolerability of a PARP inhibitor in combination with Gemcitabine in pancreatic cancer [database on the Internet]. Available from https://clinicaltrials.gov/ct2/show/NCT00515866. Identifier: NCT01585805.
104. Hakam A, Fang Q, Karl R, Coppola D. Coexpression of IGF-1R and c-Src proteins in human pancreatic ductal adenocarcinoma. Dig Dis Sci. 2003;48(10):1972–8.
105. Bergmann U, Funatomi H, Yokoyama M, Beger HG, Korc M. Insulin-like growth factor I overexpression in human pancreatic cancer: evidence for autocrine and paracrine roles. Cancer Res. 1995;55(10):2007–11.
106. Vaccaro V, Melisi D, Bria E, Cuppone F, Ciuffreda L, Pino MS, et al. Emerging pathways and future targets for the molecular therapy of pancreatic cancer. Expert Opin Ther Targets. 2011;15(10):1183–96.
107. Kindler HL, Richards DA, Garbo LE, Garon EB, Stephenson JJ Jr, Rocha-Lima CM, et al. A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer. Ann Oncol. 2012;23(11):2834–42.
108. Fuchs CS, Azevedo S, Okusaka T, Van Laethem JL, Lipton LR, Riess H, et al. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial. Ann Oncol. 2015;26(5):921–7.
109. Tabernero J, Chawla SP, Kindler H, Reckamp K, Chiorean EG, Azad NS, et al. Anticancer activity of the type I insulin-like growth factor receptor antagonist, ganitumab, in combination with the death receptor 5 agonist, conatumumab. Target Oncol. 2015;10(1):65–76.
110. Kelley SK, Ashkenazi A. Targeting death receptors in cancer with Apo2L/TRAIL. Curr Opin Pharmacol. 2004;4(4):333–9.
111. Philip PA, Goldman B, Ramanathan RK, Lenz HJ, Lowy AM, Whitehead RP, et al. Dual blockade of epidermal growth factor receptor and insulin-like growth factor receptor-1 signaling in metastatic pancreatic cancer: phase Ib and randomized phase II trial of gemcitabine, erlotinib, and cixutumumab versus gemcitabine plus erlotinib (SWOG S0727). Cancer. 2014;120(19):2980–5.
112. Morris JP, Wang SC, Hebrok M. KRAS, Hedgehog, Wnt and the twisted developmental biology of pancreatic ductal adenocarcinoma. Nat Rev Cancer. 2010;10(10):683–95.
113. El-Khoueiry ABNY, Yang D, Cole S, Kahn M, Zoghbi M, Berg J, Fujimori M, Inada T, Kouji H, Lenz H. A phase I first-in-human study of PRI-724 in patients (pts) with advanced solid tumors. 2013 ASCO Annual Meeting. 2013;J Clin Oncol 31, 2013 (suppl; abstr 2501). Available through: http://meetinglibrary.asco.org/content/115980-132.
114. Prism Pharma Co. Ltd. Safety and Efficacy Study of PRI-724 Plus Gemcitabine in Subjects With Advanced or Metastatic Pancreatic Adenocarcinoma. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01764477.
115. Shi Q, Le X, Abbruzzese JL, Peng Z, Qian CN, Tang H, et al. Constitutive Sp1 activity is essential for differential constitutive expression of vascular endothelial growth factor in human pancreatic adenocarcinoma. Cancer Res. 2001;61(10):4143–54.
116. Trachte AL, Suthers SE, Lerner MR, Hanas JS, Jupe ER, Sienko AE, et al. Increased expression of alpha-1-antitrypsin, glutathione S-transferase pi and vascular endothelial growth factor in human pancreatic adenocarcinoma. Am J Surg. 2002;184(6):642–7; discussion 7-8.
117. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42.
118. Kindler HL, Friberg G, Singh DA, Locker G, Nattam S, Kozloff M, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2005;23(31):8033–40.
119. Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol. 2010;28(22):3617–22.
120. Ko AH, Venook AP, Bergsland EK, Kelley RK, Korn WM, Dito E, et al. A phase II study of bevacizumab plus erlotinib for gemcitabine-refractory metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2010;66(6):1051–7.
121. Van Cutsem E, Vervenne WL, Bennouna J, Humblet Y, Gill S, Van Laethem JL, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol. 2009;27(13):2231–7.
122. Ko AH, Youssoufian H, Gurtler J, Dicke K, Kayaleh O, Lenz HJ, et al. A phase II randomized study of cetuximab and bevacizumab alone or in combination with gemcitabine as first-line therapy for metastatic pancreatic adenocarcinoma. Investig New Drugs. 2012;30(4):1597–606.
123. Starling N, Watkins D, Cunningham D, Thomas J, Webb J, Brown G, et al. Dose finding and early efficacy study of gemcitabine plus capecitabine in combination with bevacizumab plus erlotinib in advanced pancreatic cancer. J Clin Oncol. 2009;27(33):5499–505.

124. Watkins DJ, Starling N, Cunningham D, Thomas J, Webb J, Brown G, et al. The combination of a chemotherapy doublet (gemcitabine and capecitabine) with a biological doublet (bevacizumab and erlotinib) in patients with advanced pancreatic adenocarcinoma. The results of a phase I/II study. Eur J Cancer. 2014;50(8):1422–9.
125. Dean E, Middleton MR, Pwint T, Swaisland H, Carmichael J, Goodege-Kunwar P, et al. Phase I study to assess the safety and tolerability of olaparib in combination with bevacizumab in patients with advanced solid tumours. Br J Cancer. 2012;106(3):468–74.
126. Kindler HL, Ioka T, Richel DJ, Bennouna J, Letourneau R, Okusaka T, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. Lancet Oncol. 2011;12(3):256–62.
127. Kindler HL, Wroblewski K, Wallace JA, Hall MJ, Locker G, Nattam S, et al. Gemcitabine plus sorafenib in patients with advanced pancreatic cancer: a phase II trial of the University of Chicago Phase II Consortium. Investig New Drugs. 2012;30(1):382–6.
128. Fukasawa M, Korc M. Vascular endothelial growth factor-trap suppresses tumorigenicity of multiple pancreatic cancer cell lines. Clin Cancer Res. 2004;10(10):3327–32.
129. Rougier P, Riess H, Manges R, Karasek P, Humblet Y, Barone C, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. Eur J Cancer. 2013;49(12):2633–42.
130. Dragovich T, Laheru D, Dayyani F, Bolejack V, Smith L, Seng J, et al. Phase II trial of vatalanib in patients with advanced or metastatic pancreatic adenocarcinoma after first-line gemcitabine therapy (PCRT O4-001). Cancer Chemother Pharmacol. 2014;74(2):379–87.
131. Dragovich T, Burris H 3rd, Loehrer P, Von Hoff DD, Chow S, Stratton S, et al. Gemcitabine plus celecoxib in patients with advanced or metastatic pancreatic adenocarcinoma: results of a phase II trial. Am J Clin Oncol. 2008;31(2):157–62.
132. Tiltan Pharma Ltd. A clinical trial of anti-angiogenic drug combination Tl-118 for pancreatic cancer patients who are starting Gemcitabine treatment. In: Clinicaltrialsgov. Available in: https://clinicaltrials.gov/ct2/show/NCT01509911.
133. Luo G, Long J, Zhang B, Liu C, Xu J, Ni Q, et al. Stroma and pancreatic ductal adenocarcinoma: an interaction loop. Biochim Biophys Acta. 2012;1826(1):170–8.
134. Mahadevan D, Von Hoff DD. Tumor-stroma interactions in pancreatic ductal adenocarcinoma. Mol Cancer Ther. 2007;6(4):1186–97.
135. Kikuta K, Masamune A, Watanabe T, Ariga H, Itoh H, Hamada S, et al. Pancreatic stellate cells promote epithelial-mesenchymal transition in pancreatic cancer cells. Biochem Biophys Res Commun. 2010;403(3-4):380–4.
136. Sarker D, Molife R, Evans TR, Hardie M, Marriott C, Butzberger-Zimmerli P, et al. A phase I pharmacokinetic and pharmacodynamic study of TKI258, an oral, multitargeted receptor tyrosine kinase inhibitor in patients with advanced solid tumors. Clin Cancer Res. 2008;14(7):2075–81.
137. Galsky MD, Posner M, Holcombe RF, Lee KM, Misiukiewicz K, Tsao CK, et al. Phase Ib study of dovitinib in combination with gemcitabine plus cisplatin or gemcitabine plus carboplatin in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2014;74(3):465–71.
138. Roswell Park Cancer Institute. Dovitinib Lactate, Gemcitabine hydrochloride, and Capecitabine in treating patients with advanced or metastatic solid tumors, pancreatic cancer and biliary cancers. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01497392.
139. AB Science. A phase 3 study to compare efficacy and safety of Masitinib in combination with Gemcitabine, to Placebo in combination with Gemcitabine, in treatment of patients with advanced/metastatic pancreatic cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/show/NCT00789633.
140. Bramhall SR, Rosemurgy A, Brown PD, Bowry C, Buckels JA. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. J Clin Oncol. 2001;19(15):3447–55.
141. Bramhall SR, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JA. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. Br J Cancer. 2002;87(2):161–7.
142. Hingorani SR, Harris WP, Beck JT, Berdov BA, Wagner SA, Pshevlotsky EM, et al. Phase Ib Study of PEGylated recombinant human Hyaluronidase and Gemcitabine in patients with advanced pancreatic cancer. Clin Cancer Res. 2016;22:2848.
143. Halozyme Inc. A Study of PEGylated recombinant human Hyaluronidase in combination with Nab-Paclitaxel Plus Gemcitabine compared with Placebo Plus Nab-Paclitaxel and Gemcitabine in participants with Hyaluronan-High Stage IV previously untreated Pancreatic Ductal Adenocarcinoma. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT02715804.
144. Therapeutics H. Study of Gemcitabine + PEGPH20 vs Gemcitabine alone in stage IV previously untreated pancreatic cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01453153.
145. Group SO. S1313, Combination chemotherapy with or without PEGPH20 in treating patients with newly diagnosed metastatic pancreatic cancer. In: Clinicaltrialsgov. Available through: https://clinicaltrials.gov/ct2/show/NCT01959139.
146. Lu J, Yoshimura K, Goto K, Lee C, Hamura K, Kwon O, et al. Nanoformulation of Geranylgeranyltransferase-I inhibitors for cancer therapy: liposomal encapsulation and pH-dependent delivery to cancer cells. PLoS One. 2015;10(9):e0137595.
147. Meng H, Zhao Y, Dong J, Xue M, Lin YS, Ji Z, et al. Two-wave nanotherapy to target the stroma and optimize gemcitabine delivery to a human pancreatic cancer model in mice. ACS Nano. 2013;7(11):10048–65.
148. Kumar V, Mondal G, Slavik P, Rachagani S, Batra SK, Mahato RI. Codelivery of small molecule hedgehog inhibitor and miRNA for treating pancreatic cancer. Mol Pharm. 2015;12(4):1289–98.
149. Lucero-Acuna A, Jeffery JJ, Abril ER, Nagle RB, Guzman R, Pagel MD, et al. Nanoparticle delivery of an AKT/PDK1 inhibitor improves the therapeutic effect in pancreatic cancer. Int J Nanomedicine. 2014;9:5653–65.
150. Jiang G, Qiu W, DeLuca PP. Preparation and in vitro/in vivo evaluation of insulin-loaded poly(acryloyl-hydroxyethyl starch)-PLGA composite microspheres. Pharm Res. 2003;20(3):452–9.
151. Kobes JE, Daryaei I, Howison CM, Bontrager JG, Sirianni RW, Meuillet EJ, et al. Improved treatment of pancreatic cancer with drug delivery nanoparticles loaded with a novel AKT/PDK1 inhibitor. Pancreas. 2016;45:1158.
152. Spring BQ, Bryan Sears R, Zheng LZ, Mai Z, Watanabe R, Sherwood ME, et al. A photoactivable multi-inhibitor nanoliposome for tumour control and simultaneous inhibition of treatment escape pathways. Nat Nanotechnol. 2016;11(4):378–87.
153. Galasso M, Sandhu SK, Volinia S. MicroRNA expression signatures in solid malignancies. Cancer J. 2012;18(3):238–43.
154. Zhang B, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. Dev Biol. 2007;302(1):1–12.
155. Iorio MV, Croce CM. MicroRNAs in cancer: small molecules with a huge impact. J Clin Oncol. 2009;27(34):5848–56.
156. Bentwich I, Avniel A, Karov Y, Aharonov R, Gilad S, Barad O, et al. Identification of hundreds of conserved and nonconserved human microRNAs. Nat Genet. 2005;37(7):766–70.

157. Carthew RW. Gene regulation by microRNAs. Curr Opin Genet Dev. 2006;16(2):203–8.
158. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, et al. MicroRNA gene expression deregulation in human breast cancer. Cancer Res. 2005;65(16):7065–70.
159. Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, et al. RAS is regulated by the let-7 microRNA family. Cell. 2005;120(5):635–47.
160. Michael MZ, SM OC, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res. 2003;1(12):882–91.
161. Jiao LR, Frampton AE, Jacob J, Pellegrino L, Krell J, Giamas G, et al. MicroRNAs targeting oncogenes are down-regulated in pancreatic malignant transformation from benign tumors. PLoS One. 2012;7(2):e32068.
162. Yu S, Lu Z, Liu C, Meng Y, Ma Y, Zhao W, et al. miRNA-96 suppresses KRAS and functions as a tumor suppressor gene in pancreatic cancer. Cancer Res. 2010;70(14):6015–25.
163. Zhao WG, Yu SN, Lu ZH, Ma YH, Gu YM, Chen J. The miR-217 microRNA functions as a potential tumor suppressor in pancreatic ductal adenocarcinoma by targeting KRAS. Carcinogenesis. 2010;31(10):1726–33.
164. Abue M, Yokoyama M, Shibuya R, Tamai K, Yamaguchi K, Sato I, et al. Circulating miR-483-3p and miR-21 is highly expressed in plasma of pancreatic cancer. Int J Oncol. 2015;46(2):539–47.
165. Li A, Omura N, Hong SM, Vincent A, Walter K, Griffith M, et al. Pancreatic cancers epigenetically silence SIP1 and hypomethylate and overexpress miR-200a/200b in association with elevated circulating miR-200a and miR-200b levels. Cancer Res. 2010;70(13):5226–37.
166. Ma C, Huang T, Ding YC, Yu W, Wang Q, Meng B, et al. MicroRNA-200c overexpression inhibits chemoresistance, invasion and colony formation of human pancreatic cancer stem cells. Int J Clin Exp Pathol. 2015;8(6):6533–9.
167. Lu Y, Lu J, Li X, Zhu H, Fan X, Zhu S, et al. MiR-200a inhibits epithelial-mesenchymal transition of pancreatic cancer stem cell. BMC Cancer. 2014;14:85.
168. Singh S, Chitkara D, Kumar V, Behrman SW, Mahato RI. miRNA profiling in pancreatic cancer and restoration of chemosensitivity. Cancer Lett. 2013;334(2):211–20.
169. Ko AH, Tempero MA, Shan YS, Su WC, Lin YL, Dito E, et al. A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. Br J Cancer. 2013;109(4):920–5.
170. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;387(10018):545–57.
171. Borad MJ, Reddy SG, Bahary N, Uronis HE, Sigal D, Cohn AL, et al. Randomized phase II trial of Gemcitabine Plus TH-302 versus Gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2015;33(13):1475–81.
172. Tran EJ, King MC, Corbett AH. Macromolecular transport between the nucleus and the cytoplasm: Advances in mechanism and emerging links to disease. Biochim Biophys Acta. 2014;1843(11):2784–95.
173. Fornerod M, Ohno M, Yoshida M, Mattaj IW. CRM1 is an export receptor for leucine-rich nuclear export signals. Cell. 1997;90(6):1051–60.
174. Fung HY, Chook YM. Atomic basis of CRM1-cargo recognition, release and inhibition. Semin Cancer Biol. 2014;27:52–61.
175. Mirski SE, Sparks KE, Friedrich B, Kohler M, Mo YY, Beck WT, et al. Topoisomerase II binds importin alpha isoforms and exportin/CRM1 but does not shuttle between the nucleus and cytoplasm in proliferating cells. Exp Cell Res. 2007;313(3):627–37.
176. Abraham SA, Holyoake TL. Redirecting traffic using the XPO1 police. Blood. 2013;122(17):2926–8.
177. Alt JR, Gladden AB, Diehl JA. p21(Cip1) Promotes cyclin D1 nuclear accumulation via direct inhibition of nuclear export. J Biol Chem. 2002;277(10):8517–23.
178. Henderson BR. Nuclear-cytoplasmic shuttling of APC regulates beta-catenin subcellular localization and turnover. Nat Cell Biol. 2000;2(9):653–60.
179. Ohtani N, Brennan P, Gaubatz S, Sanij E, Hertzog P, Wolvetang E, et al. Epstein-Barr virus LMP1 blocks p16INK4a-RB pathway by promoting nuclear export of E2F4/5. J Cell Biol. 2003;162(2):173–83.
180. Santiago A, Li D, Zhao LY, Godsey A, Liao D. p53 SUMOylation promotes its nuclear export by facilitating its release from the nuclear export receptor CRM1. Mol Biol Cell. 2013;24(17):2739–52.
181. Wang Y, Wang Y, Xiang J, Ji F, Deng Y, Tang C, et al. Knockdown of CRM1 inhibits the nuclear export of p27(Kip1) phosphorylated at serine 10 and plays a role in the pathogenesis of epithelial ovarian cancer. Cancer Lett. 2014;343(1):6–13.
182. Walker CJ, Oaks JJ, Santhanam R, Neviani P, Harb JG, Ferenchak G, et al. Preclinical and clinical efficacy of XPO1/CRM1 inhibition by the karyopherin inhibitor KPT-330 in Ph+ leukemias. Blood. 2013;122(17):3034–44.
183. Abdul Razak AR, Mau-Soerensen M, Gabrail NY, Gerecitano JF, Shields AF, Unger TJ, et al. First-in-class, first-in-human phase I study of Selinexor, a selective inhibitor of nuclear export, in patients with advanced solid tumors. J Clin Oncol. 2016;34:4142.
184. Barbara Ann Karmanos Cancer Institute. Selinexor, Gemcitabine Hydrochloride, and Paclitaxel Albumin-stabilized nanoparticle formulation in treating patients with metastatic pancreatic cancer. In: Clinicaltrialsgov.Available through: https://clinicaltrials.gov/ct2/show/NCT02178436.

Improving Clinical Trial Design in Gastrointestinal Oncology

28

Ajlan Atasoy and Murielle Mauer

Introduction

Gastrointestinal (GI) malignancies collectively constitute the most common cancers encountered worldwide [1, 2]. Decades of large randomized international clinical trials of cytotoxic therapies led to substantial improvements in survival rates especially in resectable gastrointestinal tract cancers [3–7]. However, despite advances in multidisciplinary management and personalized medicine, most patients face incurable disease.

It is crucial to incorporate the rapid developments in both cancer diagnostics and therapeutics into gastrointestinal trial design, and to translate results more quickly to patient care while maintaining the reliability and reproducibility of findings. These aims require clinical and basic scientists to work in close collaboration with experts in methodology to develop sophisticated, dependable, and feasible designs.

A crucial step in conducting a good clinical trial is to prospectively describe all key aspects in a well-written protocol [8]. This step is key both for scientific rigor and successful recruitment and conduct. The protocol should describe all the objectives in detail. The statistical design should be prospectively and clearly defined. The important sections in a particular protocol vary depending on the treatment modalities and the statistical design used in the particular trial. All relevant treatment modalities, toxicity guidelines, and the translational research should be described in designated sections. The data quality, which may be challenging to achieve in large multicenter and international trials, can be enhanced by a well-written protocol. Good data quality is not only essential for the credibility of the study, but more importantly, it is an ethical obligation [9, 10]. Nevertheless, despite the improvements in the processes put in place to protect the integrity and validity of the results as well as to protect the trial's participants during the conduct of a clinical trial—such as the monitoring of the accumulating data through independent data monitoring committees (IDMCs)—other challenges have emerged in the field of clinical research.

Since the human genome was sequenced, the number of compounds in development has increased by 62% and total research and development expenditures have doubled. The increased complexity and cost of clinical trials did not necessarily translate into higher success rates. An analysis by the Centre for Medicines Research in the United Kingdom has concluded that the failure rate for drugs in phase II and III clinical trials has been rising since 2008 [11, 12]. In particular, drugs in development for oncology indications had the lowest overall clinical trial success rate of all therapeutic areas in development since 2003. As a result, the rising cost of incremental gains in health benefits is unsustainable within an environment of strained budgets [13]. Recently, biomarker-driven approaches have enabled some success in distinct subgroups. The year 2017 witnessed the highest number of oncology drug approvals by the US Food and Drug Administration (FDA) and introduction of checkpoint inhibitors into clinical practice for certain biomarker-defined GI cancers. That year marked a milestone in oncology with the tissue-agnostic approval of pembrolizumab, a checkpoint inhibitor, in the treatment of metastatic solid tumors carrying microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) by the FDA. This was shortly followed by the accelerated approval for nivolumab monotherapy in previously treated patients with MSI-H/dMMR metastatic colorectal cancer (mCRC). Treatment paradigms for gastric and hepatocellular cancers are also witnessing a shift globally, with new approvals for treatment of gastric and hepatocellular cancer in the United States and East Asia [14].

The delay in carrying new agents from early development to clinical practice is a growing concern among both patients

A. Atasoy (✉)
European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium

Research and Development, Oncology Clinical Development, Bristol-Myers Squibb, Lawrenceville, NJ, USA

M. Mauer
Department of Statistics, European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_28

and physicians. The average time for development of a new agent was reported to be approximately 7.6 years for oncological compounds [15]. This time takes into account clinical trial development and new drug registration.

Designing clinical trials that bring more value to the society and to patients requires using appropriate study endpoints and targeting more ambitious increments in treatment benefit. Major strategies to decrease failure rates in phase II and phase III trials include improving patient selection, pursuing early clinical trials demonstrating target engagement or efficacy (the so-called "proof of concept" trials), and enabling the earlier termination of the molecules that will not have the required activity [16, 17]. Innovative and flexible trial designs that would allow real-time learning and adaptations to the data in hand (among these, the so-called "adaptive" designs) were proposed to make the research approach more robust and less prone to failure [18].

Adaptive licensing, such as the European Medicines Agency's (EMA) adaptive pathways approach, may greatly improve timely access for patients to new medicines in areas of high medical need [13]. Such approaches require the collection, analysis, and interpretation of real-life data to supplement clinical trial data and confirm the benefit-risk balance of a product, following a conditional approval based on early data (using surrogate endpoints). They also require earlier involvement of patients and health-technology-assessment bodies during discussions in drug development.

Finally, new forms of multidisciplinary partnerships and partnerships between academia and industry will be needed to benefit from the expertise of several partners and to combine efforts alongside with cost-sharing models [19, 20].

Magnitude of Meaningful Clinical Benefit and Study Endpoints

Both the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have deemed it important to define value and clinical benefit in cancer care and drug development. The ASCO Cancer Research Committee has drawn attention to the need to raise the bar for clinical trials by defining clinically meaningful outcomes. In gastrointestinal oncology, two working groups, composed of experts in carcinomas of the pancreas and colon, respectively, have proposed to define the magnitude of the benefit that would be considered clinically meaningful [21]. For a phase III trial in metastatic pancreatic cancer, relevant goals would be to increase median survival of 8–9 months in gemcitabine- or gemcitabine/nab-paclitaxel-eligible patients by 3–4 months (hazard ratio [HR] = 0.6–0.75) and of 10–11 months in the FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin)-eligible patients by 4–5 months (HR = 0.67–0.69). For a phase III trial in metastatic colorectal cancer, a clinically relevant objective would be to target an HR = 0.67 in patients with disease progression following prior therapies or for a patient who is not a candidate for standard second- or third-line options.

ASCO's Value in Cancer Care Task Force launched an initiative in 2014 to define value as the combination of three factors for cancer therapy care: clinical benefit, toxicities, and costs. ASCO Value Framework was recently published to assess value in cancer care and illustrate how value is defined by the patient, the healthcare provider, and the payer [22].

The European Society of Medical Oncology (ESMO) announced its tool, the Magnitude of Clinical Benefit Scale (ESMO-MCBS), at the 2015 ASCO Annual Meeting. ESMO-MCBS is the first standard tool to offer a structured and consistent approach to grading the clinically meaningful benefit of a drug. The first version of the scale was field-tested in a range of settings and scenarios in Europe for 77 cancer drugs across 10 cancer types [23]. The main points of how ESMO-MCBS addresses benefit and endpoints can be listed as follows:

- Cure is considered to be more important than deferral of death.
- Direct endpoints such as survival and quality of life take precedence over surrogates such as progression-free survival or objective response rate.
- Disease-free survival in potential curable disease is a more valid surrogate than progression-free survival or response rate in non-curative disease.
- Interpretation of the evidence of benefit derived from surrogate outcomes (such as progression-free survival) may be influenced by secondary outcome data.

Separate evaluation algorithms were created for curative and non-curative settings, some of which have since been updated in ESMO-MCBS version 1.1 [24]. Cost was not taken into account in ESMO-MCBS due to the significant heterogeneity in costs across Europe. The goal was to assign the highest grade to trials with adequate power for a relevant magnitude of benefit and to make grade adjustment to reflect the observed magnitude of benefit. Different threshold values for HR and absolute gains for survival, progression-free survival (PFS), and disease-free survival (DFS) were discussed and explored through simulations to adequately reflect the expert opinion of the oncology community. The implemented combined threshold for the hazard ratio and the minimum observed benefit were described (Table 28.1). This instrument was designed to be regularly updated with more mature data of clinical trials. Updates should be taken into consideration while developing trial design and methodology.

Table 28.1 Maximal preliminary scores

Treatments with curative intent
5% improvement of survival at ≥3-year follow-up
Improvements in DFS alone HR < 0.60 (primary end point) in studies without mature survival data
Treatments with non-curative intent
Primary outcome OS
Control ≤ 12 months
HR ≤ 0.65 *and* gain ≥ 3 months
or
Increase *in* 2-year survival alone ≥ 10%
Control > 12 months
HR ≤ 0.70 *and* gain ≥ 5 months
or
Increase *in* 3-year survival alone ≥ 10%
Primary outcome PFS
Control ≤ 6 months
HR ≤ 0.65 *and* gain ≥ 1.5 months
Control > 6months
HR ≤ 0.65 *and* gain ≥ 3 months

Adapted with permission from Table 2 in Cherny et al. [23]
DFS disease-free survival, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival

While ASCO and ESMO consider similar aspects of clinical benefits such as overall survival (OS), PFS, response rate (RR), toxicity, and quality of life (QoL), these are evaluated differently. ASCO frameworks use a hierarchy prioritizing OS, PFS, and then RR for scoring, whereas the ESMO-MCBS prioritizes the primary endpoint of the comparison. Thus, the frameworks do not measure identical constructs of clinical benefit [25]. Treatment toxicities are also accounted for differently in each framework. For example, therapies that show improvements in QoL will have a more favorable evaluation per the ESMO scale. The ASCO framework intentionally excludes QoL measurements, which are commonly derived from patient-reported outcomes, as these measures are considered by the ASCO's Value in Cancer Care Task Force to be subjective and potentially inconsistent. In contrast, if a clinical trial includes a QoL improvement as a secondary endpoint, the ESMO score can be upgraded. On the other hand, if QoL is reported as a secondary measure, but does not demonstrate improvement, the ESMO score may be downgraded.

Endpoints in the Elderly Population

While QoL assessment has become standard in clinical trials through the use of validated patient-reported outcome instruments, incorporating QoL endpoints into the trial design remains very challenging. In the context of an aging population, well-established endpoints for clinical research may not be as relevant to older cancer patients because of competing risks of death and potentially increased impact of therapy on global functioning and quality of life [26]. Co-primary endpoints or composite endpoints could be considered to capture more than efficacy alone. However, depending on the objective, whether it is to get positive results for at least one or all co-primary endpoints, the type I or II error must be adjusted for multiple testing, which necessitates an increase of sample size. Composite endpoints allow the integration of multiple dimensions in addition to efficacy (e.g., QoL, evolution of functionality) into the definition of treatment benefit. A composite endpoint consists of multiple single endpoints that are combined so that an event is indicated if any of the endpoints occurs. Composite endpoints provide advantages in randomized controlled trials involving older patients with cancer, such as simplicity of using a single endpoint (i.e., the composite endpoint) and increased statistical power from the higher number events related to the multiple combined endpoints.

Composite endpoints are not feasible in all settings, but they are justified if the individual components of the composite are clinically meaningful and of similar relative importance to clinical care. QoL and preservation of functional capacity and independence are important for the older population and should be included more often as endpoints in clinical trials in this population. The European Organization for Research and Treatment of Cancer (EORTC) has developed a minimal data set for geriatric assessment to be included in clinical trials. Similarly, the Cancer and Leukemia Group B (CALGB) has also demonstrated the feasibility of a mainly self-administered tool in their trials [27, 28]. Other geriatric assessment options are also available, and it is important to continue international discussions on this topic [29, 30].

Surrogate Endpoints

Overall Survival

Overall survival is clearly the most straightforward and clinically meaningful endpoint for later phase, confirmatory trials. However, it requires large studies and extended follow-up and this might delay the impact of trial outcome on clinical practice and drug development when OS is selected as the primary endpoint. In addition, OS includes non-cancer deaths, and it is debated whether it may potentially be affected by crossover and by the growing number of therapeutically active options in second and subsequent lines [31].

Aside from better patient selection and using innovative clinical trial designs, identifying proper surrogate endpoints has been utilized as a means to expedite the drug approval process by the regulatory authorities [32]. Clinicians have defined a surrogate endpoint as an alternative endpoint (such as a shrinking tumor or lower biomarker levels or precursor events) that can be an indicator or sign that the treatment

works and can be used as a substitute for a clinically meaningful endpoint that directly measures survival, function, or quality of life [33]. However, a treatment effect on a surrogate endpoint—e.g., tumor shrinkage (likely transient)—does not always translate into patients' symptom relief or prolongation of survival. Strict criteria have been developed to validate surrogate endpoints [34]. Besides the biological plausibility of a surrogate, a quantitative assessment of the strength of evidence for surrogacy is necessary. The prognostic value of the surrogate must be demonstrated, along with the evidence that treatment effect on the surrogate reliably predicts treatment effect on the clinical outcome.

Disease-Free Survival and Progression-Free Survival

Recurrence/disease-free survival and PFS have been utilized as surrogates for OS to determine effective therapy with shorter follow-up. As an example, by using DFS as the primary endpoint, the MOSAIC trial (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) was able to establish the current standard adjuvant treatment approach in colon adenocarcinoma 6 years before the OS benefit was proven [7, 35]. The OS benefit was later confirmed with the updated 10-year analysis [36]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial also used 3-year DFS as primary endpoint, and the results indicated a similar magnitude of benefit [37, 38]. However, even though there was a trend toward better OS in initial OS analysis [39], the updated analysis with longer follow-up showed that OS was similar between treatment groups (HR 0.88; 95% CI, 0.75 to 1.02; $p = 0.08$). Therefore, an "early" treatment benefit on DFS or PFS may not translate into a definitive benefit on OS in all settings. The use of surrogate outcomes should be limited to situations where a surrogate has demonstrated robust ability to predict meaningful benefits, or where cases are dire, rare or with few treatment options. In both cases, surrogates must be used only when continuing studies examining hard endpoints have been fully recruited [40].

The appropriateness of choosing surrogate endpoints in GI cancers has been evaluated by expert groups in the past couple decades. In 2005, Sargent et al. reported the results of a pooled analysis of individual patient data from 20,898 patients on adjuvant colon cancer trials and demonstrated "a consistent and strong association" between the endpoints of 3-year DFS and 5-year OS [41]. This analysis, known as the ACCENT (Adjuvant Colon Cancer Endpoints) analysis, included a total of 18 randomized phase III clinical trials including 43 different treatment arms. The trials were conducted from 1977 through 1999. During the 8-year follow-up period, 80% of recurrences were documented within the first 3 years. For 33 of the total 43 study arms, the difference between the 3-year DFS and the 5-year OS was less than 3%. DFS and OS were found to highly correlate both within patients and across trials. It should be kept in mind that in the era included in this study (1997–1999), the impact of the palliative systemic treatment options on survival was not as meaningful as it is today.

It is not clear, however, whether PFS is equally reliable as surrogate endpoints in advanced malignancies of the digestive tract. An earlier literature-based analysis from 39 randomized controlled trials of first-line chemotherapy in advanced colorectal cancer evaluated the correlations between PFS, time to progression (TTP), and response rate with overall survival in the first-line treatment of metastatic colorectal cancer and concluded that improvements in PFS are strongly associated with improvements in OS in this setting [42]. Buyse et al. also investigated the validity of using PFS as a surrogate for OS and reported a strong correlation between these endpoints [43]. However, it is important to remember that the definition and the assessment of disease progression have evolved with time, with more frequent and more careful radiographic and metabolic assessments using more sensitive imaging techniques [44]. Moreover, improvements in access to medical care and staging procedures have contributed to lower tumor burden upon diagnosis, which, when combined with better clinical options beyond progression, have led to less symptoms and longer survival post-progression. Statistical modeling has suggested that the association between OS and PFS becomes weaker in diseases with longer survival post-progression [45]. It is therefore no longer clear whether PFS is a reliable surrogate for OS in metastatic colorectal cancer (mCRC) in later phase trials, despite the fact it was found acceptable in principle in recent years by the FDA.

The value of these surrogate endpoints in an era of precision medicine is yet to be established, especially in immune-oncology (IO) trials. It remains to be seen whether the durability of response with checkpoint inhibitors can be reliably shown to translate into OS benefit in IO-sensitive subgroups of GI cancers.

Objective Tumor Response and Tumor Shrinkage

Aside from PFS and DFS, objective response rate has also been explored as a surrogate endpoint. In mCRC, some endpoints of interest with anti-EGFR therapy have been early tumor shrinkage (ETS) and depth of response (DpR). While ETS and DpR are proposed more recently as surrogates for OS than PFS, they seem to correlate with certain clinical outcomes according to some retrospective analyses [46]. Early tumor shrinkage, which is measured at 6 weeks of starting treatment, has been considered by some to be an early indicator of high treatment sensitivity [47–50]. While these are not appropriate as primary endpoints especially in later phase trials, it may be helpful to collect more data on these endpoints by keeping them among secondary endpoints in trials with targeted therapy for mCRC.

Clearly the primary outcome measure in definitive trials should remain a clinical event relevant to the patient, or an endpoint that measures directly how a patient feels, functions, or survives. At the same time, the establishment of more reliable early endpoints for assessing treatment response and long-term benefit would guarantee that appropriate decisions are taken during the early phases of drug development and ensure a timely transition between phases. These early indicators do not have to reach the same requirements for surrogacy as the endpoints for the approval of cancer drugs.

Response evaluation criteria in solid tumor (RECIST) has been widely used for the early evaluation of the change in tumor burden due to its simplicity and reproducibility and the need for standardizing the assessment over the different clinical trials. However, with the increasing use of novel targeted agents and immune-modulating agents and the development of high imaging techniques, limitations have been noted with RECIST version 1.1, which was developed primarily for cytotoxic agents and anatomic imaging. Identified areas of potential weakness included: (1) lack of incorporation of potential early indicators of response such as functional imaging, (2) lack of validation in rarer tumor types, and (3) lack of validation for novel (targeted) agents and immunotherapies [51]. To incorporate more modern, imaging-based response evaluation, the positron emission tomography (PET) response criteria in solid tumors (PERCIST) 1.0 has been proposed [52], but it still requires proper validation. As a consequence, the RECIST Working Group has expanded the RECIST data warehouse to include trials of targeted agents as well as trials including functional imaging. Availability of guidelines for PET imaging allows the inclusion of this functional tumor imaging technique in large multicenter trials.

The immune-related response criteria (irRC) based on the World Health Organization (WHO) criteria [48] and a subsequent adaptation of these based on the RECIST criteria (irRECIST criteria) were developed to limit declaring treatment failure prematurely in a given patient (Table 28.2) [53]. The irRECIST criteria are based on irRC criteria adapted for unidimensional measurements, as outlined in Nishino et al. [54]. These criteria lack proper validation. Therefore, the

Table 28.2 Summary of RECIST, irRECIST, and iRECIST criteria

	RECIST 1.1	irRECIST	iRECIST
Target and nontarget lesions	Sum of the longest diameters of target lesions (unidimensional) Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions) Maximum of five lesions (two per organ)		
New lesion	Represents PD	Does not correspond to a formal progression The longest diameter will be added to the total measured tumor burden of all target lesions at baseline	Does not correspond to a formal progression Is not incorporated in tumor burden
CR	Disappearance of all target and nontarget lesions Nodal short axis diameter < 10 mm No new lesions		
PR	Decrease of ≥30% in tumor burden relative to baseline Non-unequivocal progression of nontarget lesions No new lesions		
SD	Neither PR nor PD		
PD	Increase ≥20% of the sum of LD compared with nadir (minimum 5 mm) or progression of nontarget lesions or new lesion	*irPD* Increase ≥20% (minimum 5 mm) in TMTB compared with nadir or progression of nontarget lesions or new lesion	*iUPD* Increase ≥20% of the sum of LD compared with nadir (minimum 5 mm) or progression of nontarget lesions or new lesion
		Confirmation of progression recommended minimum 4 weeks after the first irPD assessment	Confirmation of progression recommended minimum 4 weeks after the first iUPD assessment
Confirmed PD	Not required	New unequivocal progression or worsened progression from initial PD visit Appearance of another new lesion	*iCPD* Increased size of target or nontarget lesions Increase in the sum of new target lesions >5 mm Progression of new nontarget lesions Appearance of another new lesion

Adapted from [53]

RECIST response evaluation criteria in solid tumor, *CR* complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease, *iUPD* unconfirmed progressive disease, *iCPD* confirmed progressive disease, *LD* longest diameters, *TMTB* total measured tumor burden

RECIST working group has developed a consensus guideline iRECIST [55]. This guideline not only provides response criteria for use in immunotherapy trials, but also aims to ensure consistent data collection to facilitate further validation or future revision of iRECIST as needed.

Pathological Response

In the neoadjuvant setting, pathological response to therapy will require further validation as well. In gastric adenocarcinomas, the Becker regression grading is based on the percentage area of viable tumor at the primary tumor site in relation to the area of the identifiable tumor bed. Patients are classified into the following categories:

- Regression score 1a (complete response): no residual tumor
- Regression score 1b (subtotal regression): less than 10% residual tumor
- Regression score 2 (partial tumor regression): 10–50% residual tumor
- Regression score 3 (minimal or no regression): more than 50% residual tumor

Tumor regression (regression scores 1a and 1b) was found to be an independent prognostic factor for survival in a multivariate analysis of tumor regression, ypT/N/L category, resection status, grading, and Lauren's classification [56]. While pathologic complete response following neoadjuvant chemotherapy was reported to indicate favorable survival outcome [57], subtotal regression (<10% residual tumor cells) did not show differences in outcomes compared to less extent of tumor regression [58]. The prognostic value of histopathological tumor regression remains not well characterized in gastric cancer.

Precision Medicine in Clinical Trials

Prospectively defining the patient population based on validated molecular biomarkers gained significance with the advances in precision medicine research. This selectivity aims to improve the benefit-risk balance by treating only patients who may benefit from a new treatment strategy and allow a more personalized treatment approach, thus providing better clinical value. Moreover, biomarker-driven designs allow more efficient clinical trials using fewer subjects.

Recent developments in "omics" technologies bring promise in better characterization of diseases, which may provide both prognostic and predictive information, allowing the selection of the most beneficial therapies. An omics-based test is defined as "an assay composed of or derived from multiple molecular measurements and interpreted by a fully specified computational model to produce a clinically actionable result" [59]. It refers to a broad array of technologies that have been increasingly used in cancer detection, risk stratification of disease, and prediction of response to therapy. These include genomics, proteomics, epigenomics, and transcriptomics. However, the clinical translation of these developments has been slow despite the rapidly growing body of data. The process of bringing omics from bench to bedside requires rigorous efforts in development and validation.

It is important to keep in mind that not all assays currently used in clinical trials are properly validated, which in turn influences the validity of some of the biomarkers incorporated into drug trials. The US National Cancer Institute (NCI), in collaboration with omics experts and based on principles set forth by the Institute of Medicine, developed a checklist of criteria to be used as guidelines to promote quality in omics technology that will be used in clinical trials [59]. It was suggested by the developers of this 30-point checklist that these criteria should be applied when incorporating a tumor biomarker test into any clinical trial that prospectively evaluates its clinical utility and that they should also be for assessing study quality and evidence strength by funding bodies and journals evaluating such studies. The checklist is being used to evaluate proposals for NCI-sponsored clinical trials in which omics will be used to guide therapy. It contains specific recommendations in the following areas:

- Specimen collection, processing, storage, etc.
- Technical issues related to omics-based assays (e.g., reagents, specimens, instrumentation, scoring methods)
- Mathematical predictive model development, specification, and preliminary performance evaluation
- Clinical trial design and conduct (e.g., rigor of statistical design, informatics plan for the data, complete specification of the omics test)
- Ethical, legal, and regulatory issues (safety and privacy of patients, intellectual property issues)

Ethics of Biomarker Identification: Mandatory Biopsies During Clinical Trial

Academic investigators and the pharmaceutical industry are increasingly interested in incorporating tissue sampling into clinical trial design when studying novel interventions. However, trial designs with mandatory research biopsies raise ethical concerns because the risk of harm to participants and the adequacy of voluntary informed consent. In consideration of such issues, the Cancer and Leukemia Group B (CALGB) Ethics Committee proposed guidelines for clinical trials involving mandatory research biopsies [60]. Any cancer clinical trial that has mandatory research biopsies

must be well designed to address the scientific question, obtain the biopsy in a way that minimizes risk to participants, and ensure that subjects are fully informed of the risks, rationale, and requirements of the study, as well as of treatment alternatives. These basic principles are regularly applied by ethics committees. Firstly, the study protocol is expected to prospectively and clearly define the rationale for the mandatory biopsies and to identify the research planned for these biopsies, what the endpoints are and whether an appropriate statistical analysis plan has been developed. Moreover, there must be a standard acceptable and intelligible language for informed consent. In addition, there is a clear need for data on anatomic sites that may be more accessible to provide realistic estimates of safety to investigators and potential trial participants. The urgency to improve these aspects were outlined in the findings of Overman et al. [61]. They reported that among the 38 clinical trials identified from their interventional radiology database as requiring mandatory research biopsy, the primary indication was correlative science in 68% of them, and only 26% had a statistical analysis plan provided in the study protocol. Site-stratified biopsy risks were explained in consent forms from only five of the studies, and the overall complication rate was 5.2%, with 0.8% being major complications. They concluded that a better representation of the risks and benefits of research biopsies in study protocols and informed consents is needed.

Traditional Clinical Trial Designs and Innovative Approaches

Clinical trials utilizing pharmaceutical agents are classically divided into phases I–IV. Earlier phase studies (phase I, I/II, and II) are designed to generate data to support and plan later phase confirmatory studies, which provide more definitive information with the potential to impact standard of care. However, the traditional clinical trial approach based on sequential, distinct phases may not be the most efficient or the most cost-effective path for drug development. Advancing clinical trial design and to move toward a more integrated view that uses adaptive design tools to increase flexibility and maximize, the use of accumulated knowledge has been considered as an important step for the future of drug development [18].

Phase I Trials

Traditionally, the main objective of phase I trials has been dose finding and to identify the side effects of a drug or drug combination [8]. The pharmacokinetics and pharmacodynamics of a drug are studied in this phase of drug testing. Classical phase I trials designs rely on a monotonic dose-toxicity relationship in order to determine the maximum tolerated dose (MTD). Typically the initial dose is very low and is increased in subsequent patients based on pre-planned steps that take the dose-limiting toxicities (DLT) into consideration. Cohorts of three to six patients are treated at each dose level. The decision to escalate the dose for the next cohort depends on whether or not any DLTs were seen at a given dose level (dose escalation studies). A phase II recommended dose is defined based on this system, and usually six or more patients are treated at the recommended dose for confirmation purposes. These are small trials, often including patients with different types of tumors.

The standard 3 + 3 dose-escalation design has been challenged in many ways [62]. Concerns have been raised about the operating characteristics of this design. First, the 3 + 3 cohort method has no explicit objective in mind, other than to find a dose that gives an observed DLT rate of no more than 33%. Therefore, the 3 + 3 cohort method produces data that give no confidence in what the actual DLT rate of any of the dose levels might be and thus little confidence in the selected MTD [63]. Another major disadvantage of this 3 + 3 design is that it may involve an excessive number of escalation steps, which may result in a large proportion of the patients treated at subtherapeutic doses, while only a few patients actually receive doses at or near the recommended dose for phase II trials [64]. Therefore, if the therapeutic window is wide and the expected toxicity is low, then rapid escalation with a novel rule- or model-based design should be employed. Several innovative phase I designs have been proposed to improve efficiency as compared to the 3 + 3 design and are summarized in Table 28.3 [63, 65]. Examples of such strategies include: accelerated titration designs [66], Bayesian model-based designs such as the Continual Reassessment Method [67], or the Escalation With Overdose Control (EWOC) method [68, 69], which is essentially a modified continual reassessment method with additional safety measures put in place to avoid exposing patients to doses that are potentially too toxic.

More than ever, the increasing number of molecularly targeted agents in early phases of drug development and the abundance of information on tumor biology presents a need for a more efficient approach to early phase trials [70]. In phase I cancer clinical trials that involved cytotoxic agents, the conventional primary endpoint was toxicity, which, with efficacy, was assumed to increase with the drug dose. Molecularly targeted agents modulate specific aberrant pathways in cancer cells while sparing normal tissues, and as such the toxicity and efficacy of these novel agents may not be dose-dependent above a certain level [64]. Demonstrating effective target inhibition in tumors was suggested as an alternative endpoint, but that type of assessment is very challenging. Moreover, traditional dose-escalation designs to identify the MTD or the biologically active dose (BAD) may

Table 28.3 Summary of classes of phase I trial designs and key references

Class	Specific design	Key features	Limitations
Algorithmic designs	3 + 3 cohort A + B cohort	Easy to use	Can overestimate MTD No explicit targeted DLT rate Small sample size leads to insufficient data Not easily extended to more complex settings
Nonparametric designs	Biased coin (BCD)	Computationally simple	Not easily extended to more complex settings
	Cumulative cohort (CCD)	Identifies MTD more reliably than algorithmic designs	
Parametric designs	Continual reassessment method (CRM)	Published software available	Computationally intensive
	Escalation with overdose control (EWOC)	Identifies MTD more reliably than algorithmic designs	Requires knowledge of statistical modeling
	Modified toxicity probability interval (mTPI)	Can be extended to more complex settings easily	

Adapted from [63]
MTD maximum tolerated dose, *DLT* dose-limiting toxicity

not be applied to cancer vaccines given that the risks of serious toxicities with therapeutic cancer vaccines are extremely low and that toxicities do not correlate with dose levels [71].

With more thoughtful design, phase I might bring in more information than mere toxicity [72]. A promising signal at this phase might even lead to getting on a fast-track in the regulatory approval process. Since ASCO first emphasized the importance of phase I trials in cancer treatment back in 1997, the landscape of oncologic research has changed tremendously [73]. The rapidly increasing number of molecularly targeted agents and immunotherapies along with advances in trial design led ASCO to issue a policy update on phase I trials [74]. It is pointed out that with newer phase I designs, researchers and drug sponsors can study signals of antitumor activity while evaluating toxicity. Newer phase I designs may also be more ethical by limiting the number of patients that may be exposed to subtherapeutic doses.

Phase II Trials

Classically, after the determination of the MTD in phase I trials, phase II trials are conducted to evaluate the antitumor activity of the drug or drug regimen, to provide a more detailed description of the toxicity. Outcome of phase II trials will lead to an informed decision whether or not to pursue the development of the treatment and whether to go for a large confirmatory phase III trial. Dose-ranging studies are often conducted as phase II trials and are designed with the objective of identifying a dose or a few doses to be used in future trials. Phase II trials are exploratory studies by nature and designed to provide information about major design elements for use in the phase III trial (statistical variability) and to project the magnitude of treatment effects.

Given the high failure rates, the increased costs of phase III trials in oncology, and the number of new drugs in early development, better design options were considered to optimize the use of resources. In this context, adaptive design approaches have revolutionized the field of clinical trial designs. Real-time learning during the trial allows adapting to the incoming data. Adaptive approaches are also promising for expediting the drug development program by efficiently combining phase II and phase III trials into seamless phase II/III trials [18].

Adaptive Phase II Trials

In their "Guidance for Industry" on "Adaptive Design Clinical Trials for Drugs and Biologics" (February 2010), the FDA acknowledged that the flexibilities offered by adaptive design trials may be particularly useful in this exploratory period of development and encouraged sponsors to gain more experience with these adaptive design methods in this setting. The definition by the FDA of an adaptive design clinical study is a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data, which is usually interim data, from subjects in the study. This distinction between adaptations that are prospectively planned and unplanned adaptations is important, given the latest trend toward designs with some unusual properties. Initially, the lack of clarity in the definition of "adaptive designs" was a source of confusion and has created controversy regarding their use [75]. For a valid implementation of an adaptive trial design, all criteria for adapting key clinical trial design parameters should be fully specified in advance.

For dose-ranging studies investigating the dose-effect relationship, using an adaptive allocation of doses—i.e., using accumulated data on responses of subjects in a trial to assign doses

that are more informative of the dose-response curve—may allow researchers to gather more information on the "interesting part" of the dose-effect curve between the smallest active dose and the highest dose. Therefore, adaptive dose-ranging study designs have become quite common and may result in power gains to detect dose response and higher precision in estimating the target dose and the dose-response curve [76]. In addition, by using outcome-adaptive randomization to favor treatment arms having more favorable outcomes based on interim data, they may also reduce the number of subjects randomized to potentially ineffective treatments.

The so-called "play-the-winner" designs using outcome-adaptive randomization in multi-arm clinical trials allow allocating patients to multiple arms based on interim efficacy findings. Such designs have been experimented with in oncology [77]. The advantage is that they may reduce the number of patients assigned to the inferior treatment arm. However, the debate regarding their operating characteristics is ongoing, as some would argue that equipoise is not maintained during the conduct of such a trial, and that with the use of early stopping rules, the benefits from a response-adaptive design relative to equal allocation are greatly lessened. In addition, they may have lower probability of selecting superior treatments as compared to equal randomization [78]. Moreover, there is a chance that insufficient information may be collected on an inferior arm, which could introduce bias into the estimation of treatment effect [79].

Innovative Biomarker-Driven Phase II Trials: Master Protocols

Two of the most commonly used designs utilizing precision medicine are basket and umbrella trials (Fig. 28.1) [80].

Basket Trials

Basket trials incorporate a histology-independent, biomarker-driven approach in clinical trial design. They are built on the assumption that a certain molecular marker predicts response to a targeted therapy independent of tumor type [81]. The intention is to conduct several parallel phase II trials. For a basket trial to succeed, the underlying molecular hypothesis should have strong data supporting it.

Among examples of basket trials in gastrointestinal oncology are the V-BASKET trial (NCT01524978) evaluating the *BRAF* inhibitor vemurafenib in non-melanoma tumors and the KEYNOTE-028 trial (NCT02054806) [82], which is a multi-cohort, non-randomized phase 1b basket trial evaluating pembrolizumab, a checkpoint inhibitor, in patients with biomarker-positive advanced solid tumors.

Challenges with these designs include feasibility issues with the low incidence of certain mutations in specific histology subtypes. For instance, the CUSTOM study, which evaluated molecular profiling and targeted therapy for advanced thoracic malignancies, only succeeded in accruing to 2 of the planned 15 arms [83], which raised questions about the fea-

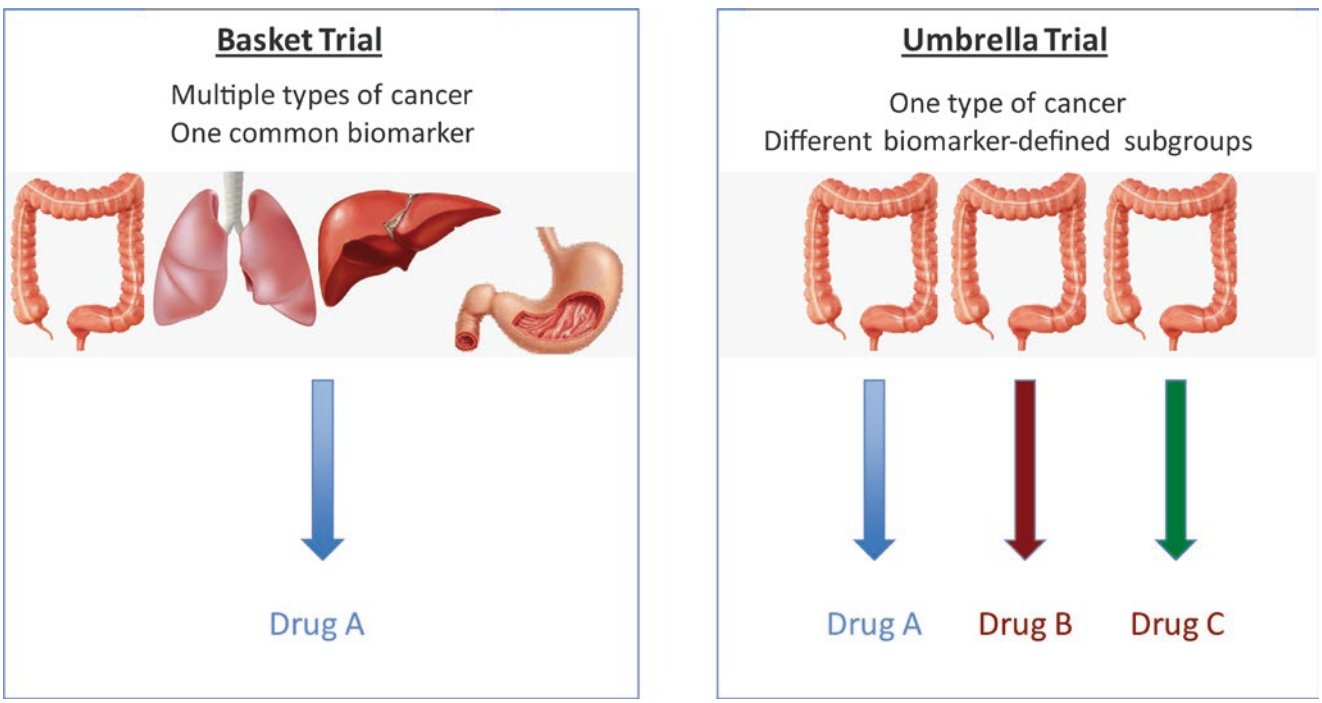


Fig. 28.1 Innovative biomarker-driven trial designs in precision oncology. (Adapted from [80]). (Reprinted with permission from Biankin et al. [96])

sibility of such an approach. Moreover, it is important to remember that having multiple trial arms increases the chance of a statistically significant result by chance alone if no proper adjustment of the type I error is applied.

Umbrella Trials

While basket trials enroll patients according to the presence of a particular biomarker or molecular alteration independently of a particular cancer type, umbrella trials aim to evaluate many treatments within a single histology. Typically, in an umbrella trial, patients with tumors from the specified cancer type are screened using a master protocol and subsequently assigned to one of several molecularly defined subprotocols with a matched targeted treatment. FOCUS4 trial (EudraCT 2012-005111-12) and MoTriColor program are examples of master protocols in GI cancers [84].

Similar to basket trials, challenges with these designs include feasibility issues with the low incidence of certain mutations in specific histology subtypes. Such studies are complex as they sometimes rely on parallel development of several drugs targeting different mutations within same histology. Various arms may be added and removed during the study conduct based on internal or external data availability and emergence of new drugs. In addition, it is not always clear to which arm patients whose tumors carry several mutations should be assigned. Ideally, rules for allocation to the different arms should be clearly described in the protocol.

As a conclusion, both baskets and umbrella trials may offer efficient solutions to drugs with predictive biomarkers in one protocol. However, feasibility issues and complexity of these designs should not be underestimated [85]. In addition while these designs may offer efficient operational strategies, the underlying statistical design in many baskets and umbrella trials is often not innovative and oftentimes as a classical phase II design (such as the A-Hern design or a two-stage Simon design) is simply applied [82]. More refined statistical designs are currently under development [86].

Phase III Clinical Trials

Phase III trials are confirmatory trials to investigate the comparative efficacy of a new treatment as compared to standard of care. Large prospective phase III randomized controlled trials (RCTs) have traditionally been assigned the highest level of evidence, with emphasis on scrutiny on trial design and conduct. They may introduce to a new standard of care and, in turn, lead to better clinical outcomes. They may lead to marketing approval of a new agent by regulatory agencies. In contrast to the exploratory trial designs described previously, the design of confirmatory or evidence-setting trials requires a promise to bring a scientifically valid conclusion. Therefore, the control of statistical errors and operational biases is of paramount importance. In regulatory applications, strong control of type I errors is required.

In a phase III trial, a two-sided type I error α(alpha) of 5% is typically used, and the required sample size is computed in order to reach adequate power 1-β(beta) (typically chosen as a value around 80–90%) to find a pre-specified target treatment benefit that is considered clinically meaningful. When a survival endpoint is used as primary endpoint of the phase III trial, treatment benefit is usually expressed in terms of a hazard ratio (HR), assuming a constant hazard over time in both the control and experimental arms through exponential distributions. For a given HR, the number of events E required in each treatment arm is approximately [87]:

$$E = \frac{2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{\left(\log \mathrm{HR}\right)^2}$$

Table 28.4 illustrates how the number of events increases in function of the target HR.

As mentioned previously, both ASCO and ESMO have drawn attention to the need to raise the bar for clinical trials and go beyond the modest increments in efficacy seen with traditional interventions. The hope is to achieve this objective through precision medicine and a better identification of patients who really benefit from a given treatment. However, while decreasing the sample size by targeting larger treatment benefit in a restricted patient population, these new approaches bring other challenges. In a trial designed to target a molecular alteration of low incidence, a huge screening effort will be required in order to include a sufficient number of patients harboring the specific molecular alteration. As an example, the Neoadjuvant Study Using Trastuzumab or Trastuzumab With Pertuzumab in Gastric or Gastroesophageal Junction Adenocarcinoma, known as the INNOVATION trial (clinicaltrials.gov NCT02205047), is investigating the added value of combining these two HER-2-targeting drugs with perioperative chemotherapy in this setting. Over a 4-year accrual period, 225 patients with HER-2-positive cancers will have to be centrally randomized. Given that approximately 10–20% of patients with gastric cancer are expected to have HER-2-positive tumors [88–90], a total of 2250 patients will have to be screened. In this context, to put in place efficient screening infrastructures will be a key driver for success.

Table 28.4 Number of events for different hazard ratios for a two-sided 5% significance level and 90% power

Hazard ratio	Number of events
0.6	81
0.7	166
0.8	423
0.9	1894

Adaptive Phase III Designs

The use of adaptive designs during the later confirmatory phase has been much more controversial than during the learning phase. The motivation for using adaptive trials in the confirmatory stage is adapting to the incoming data during the course of the trial, which might reduce the chances of trial "failure." In addition, combining "reasonable learning" with confirmation within one single trial (seamless phase II/III trials) can help to shorten the drug development timelines and allow more efficient use of sample size. The latter is particularly important in the setting of rare diseases or rare molecular alterations.

Originally, the controversy surrounding adaptive designs was centered on the inherent paradox of learning during the course of a later phase trial, which could only be considered confirmatory in the presence of pre-specified hypotheses and statistical plan. With the availability of the FDA guidance and the increasing regulatory acceptance regarding the use of more flexible designs, the debate has more recently focused on the properties and the operating characteristics of these designs. Prerequisites for the regulatory acceptance of such a design are the guarantee that the adaptation will not lead to bias that increases the chance of a false conclusion that the treatment is effective (protection of the type I error) and will not lead to positive study results that are difficult to interpret irrespective of having control of type I error.

The FDA has classified the adaptive designs into two main categories:

1. Generally well-understood adaptive designs with valid approaches to implementation. This category includes:
   (a) Adapting the study eligibility criteria based on analyses of pretreatment (baseline) data: Examination of baseline characteristics of the accumulating study population may reveal that the expected population is not enrolled or not at the desired speed. Modifications of some noncritical entry criteria may help to enter the population with the desired characteristics or allow more patients to qualify.
   (b) Adapting to maintain study power based on blinded interim analyses. The sample size or the total study duration may need to be adjusted in order to observe the required number of events and maintain power.
   (c) Adapting based on interim results of an outcome unrelated to efficacy, such as stopping a treatment arm that is too toxic.
   (d) Adapting using group sequential methods and unblinded analyses for early study termination because of either lack of benefit or demonstrated efficacy. The implementation of early stopping rules for efficacy or futility through group sequential methods is now standard practice in many modern clinical trials. This is an adaptive design in the sense that it offers a possibility for early termination with a study sample size reduced to the size accumulated at the time of an interim analysis. To protect the trial against operational bias, any leakage of information about the interim results should be avoided in case the criteria for early termination are not met. This is achieved by assigning the responsibility for monitoring comparisons of efficacy and/or safety outcomes to an independent data monitoring committee (IDMC) (ICH E9 guidance).
   (e) Adapting the data analysis plan independently of within study, between group outcome differences. The complete details of the statistical analyses are sometimes difficult to specify in advance not knowing the relevant characteristics of the final outcome data. If modifications in the data analysis plan are based on a review of these characteristics in the entire study population in a blinded manner, they do not introduce bias.
2. Adaptive study designs whose properties are less well understood. Any adaptive design approach not falling into the main category listed above is considered as "less well understood" as per this FDA classification system.

Seamless Phase II/III Trials

Seamless phase II/III trials combine "reasonable learning" with confirmation within one single confirmatory trial. The following examples can be listed:

- To first select the best dose regimen or the more promising experimental treatment among several tested based on interim data and to next confirm the superiority of the selected arm versus the standard of care (multi-arm multistage or MAMS trials) [91]
- To start to investigate the efficacy of an experimental treatment in the overall population and to then select the target population (the overall population or a predefined subgroup) depending on interim data and to next confirm the efficacy of the treatment versus the standard of care in the selected population (Adaptive Population Enrichment Trials) [92]

Sample Size Re-estimation Based on Early Observed Treatment Difference

The strategy behind adaptive sample size re-estimation based on interim-effect size is to plan for a smaller sample size under an optimistic treatment effect at the start of the clinical trial and to decide whether or not to increase it during the course of the clinical trial based on the observed treatment difference at interim analysis. Indeed, if the observed treatment effect at interim is lower than anticipated but still judged promising and clinically relevant, one may be willing to increase the sample size to be powered to detect such a treatment effect. The FDA strongly discour-

ages reducing the sample size during the course of a clinical trial, as this will reduce the precision of the treatment benefit estimate.

An example of sample size re-estimation is the promising zone design developed by Mehta and Pocock, which will partition the interim outcome into three zones: (1) an unfavorable zone, (2) a promising zone, and (3) a favorable zone, expressed equivalently in terms of the observed HR or the estimated conditional power [93]. The conditional power is the probability that the final study results will be statistically significant based on the data observed thus far, and assuming that the data still to come will follow the effect estimated from the data in hand. If the results fall into the unfavorable zone, the sample size will not be increased because the results are not judged promising and no change in the design will be made. If the results fall into the favorable zone, no change in the design will be made given that the initial sample size is considered to be sufficient to reach the desired power at final analysis. However, if the results fall in the promising zone, it will trigger an increase in sample size to raise the power against a less optimistic HR. The risk in increasing the sample size in this manner disadvantage is clear: A larger sample size will allow the detection of smaller treatment effects, even those that may not be clinically relevant. A difference will always exist between treatments, and even if negligible, there is the potential to demonstrate this negligible difference by entering an overwhelming number of patients in the clinical trial. Thus, by desiring to increase the chances of success, one might end up demonstrating a negligible treatment benefit and exposing many patients to an ultimately ineffective drug [94].

In conclusion, adaptive designs could save time and resources. However, they need extensive logistics and statistical resources. Extensive simulations need to be performed upfront to guarantee adequate operating characteristics and a strong control of the type I error in case of a confirmatory trial as well as to assess the merits of adaptive designs in comparison to better understood methods (such as early stopping rules). Finally, processes and firewalls need to be put in place upfront to protect the confidentiality of the interim results and avoid any risk of back computation of the interim results.

Phase IV Clinical Trials

Drugs that are approved as a result of phase I–III trials often require longer-term observation in phase IV studies. The true value in real-life settings can be more easily understood with these post-marketing studies, which deserve resources and efforts just as much as the earlier phase trials that initially provided the information to bring the drug to the market. As a matter of fact, the more recent EORTC approach delivers the message that focusing resources in earlier phase trials and in collecting population-based real-world data may be the approach needed in the twenty-first century to efficiently move cancer treatment forward (Fig. 28.2) [95]. Incorporating more real-life data into drug development may help to address the gap between efficacy and effectiveness and the balance between benefit and risks.

Despite its clear benefits, bringing real-life clinical data into drug development represents a major challenge for pharmaceutical companies, regulators, and health authorities. The European Union's Innovative Medicines Initiative (IMI) has officially launched its multi-stakeholder, €16.3 million GETREAL project, which is looking at new ways to integrate data from real-life settings into drug development. Real-life data is inevitably associated with the risk of biased results given the many confounding factors, which may completely distort the results. One of the aims of the GETREAL consortium is to provide recommendations on the design of

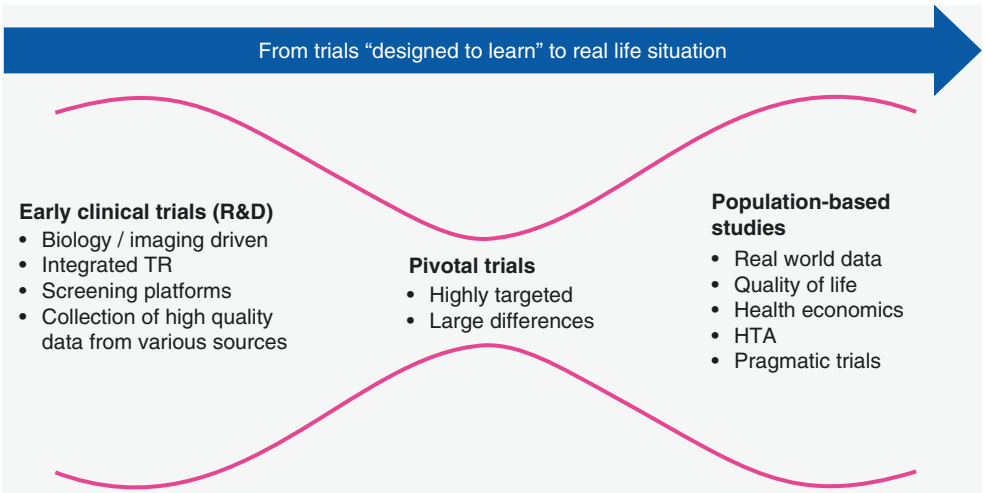


Fig. 28.2 Advancing cancer care by increasing emphasis on population-based studies. (Reprinted with permission from Burock et al. [95])

studies capable of providing information on the real-world effectiveness of medicines, including relative effectiveness, and to propose analysis methods best suited to produce unbiased results.

Conclusion

Gastrointestinal cancers collectively remain the leading cause of cancer-related death. A significant proportion of seemingly curable patients face relapse despite improvements in multidisciplinary care, and metastatic GI cancers remain incurable. Rapid developments in precision medicine bring promise but also a lot more questions, which adds to the complexity of conquering GI cancers. Moreover, with every advance, it is becoming more challenging to reliably demonstrate meaningful incremental benefit.

Innovative designs and biomarker selection or enrichment are among the key tools for cancer researchers in an era of precision medicine. However, the complexity and challenges in utilizing these advances in tools should be reviewed carefully. Moreover, while the advances in "proof-of-concept" trials enable a significant growth in the number of drug approvals and clinical trials, the value of confirmatory trials and real-world data are likely higher than before to support the reliability this rapid growth.

Electronic medical record systems continue to grow and carry the potential to generate enormous amount of real-life clinical data. Making sense of this information will require careful planning to be able to accurately give direction to cancer care.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.
3. Sargent D, Sobrero A, Grothey A, O'Connell MJ, Buyse M, Andre T, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2009;27(6):872–7.
4. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
5. Group G, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA. 2010;303(17):1729–37.
6. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090–8.
7. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27(19):3109–16.
8. DeVita VT, Lawrence TS, Rosenberg S. DeVita, Hellman, and Rosenberg's cancer: principles and practice of oncology. 10th ed. Philadelphia: Wolters Kluwer; 2014.
9. F.D.A. US. Clinical trials and human subject protection. [November 1, 2015]; Available from: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.
10. ICH. Good clinical practice (GCP). International Council for Harmonization; 1996 [cited 2015 November 1, 2015]; Available from: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html.
11. Arrowsmith J. Trial watch: phase II failures: 2008–2010. Nat Rev Drug Discov. 2011;10(5):328–9.
12. Arrowsmith J. Trial watch: phase III and submission failures: 2007–2010. Nat Rev Drug Discov. 2011;10(2):87.
13. Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. Clin Pharmacol Ther. 2012;91(3):426–37.
14. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nat Biotechnol. 2014;32(1):40–51.
15. Kaitin KI, DiMasi JA. Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000–2009. Clin Pharmacol Ther. 2011;89(2):183–8.
16. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9(3):203–14.
17. Peck RW. Driving earlier clinical attrition: if you want to find the needle, burn down the haystack. Considerations for biomarker development. Drug Discov Today. 2007;12(7–8):289–94.
18. Orloff J, Douglas F, Pinheiro J, Levinson S, Branson M, Chaturvedi P, et al. The future of drug development: advancing clinical trial design. Nat Rev Drug Discov. 2009;8(12):949–57.
19. Lacombe D, Burock S, Meunier F. Academia-industry partnerships: are we ready for new models of partnership?: the point of view of the EORTC, an academic clinical cancer research organisation. Eur J Cancer. 2013;49(1):1–7.
20. Lacombe D, Tejpar S, Salgado R, Cardoso F, Golfinopoulos V, Aust D, et al. European perspective for effective cancer drug development. Nat Rev Clin Oncol. 2014;11(8):492–8.
21. Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32(12):1277–80.
22. Schnipper LE, Davidson NE, Wollins DS, Tyne C, Blayney DW, Blum D, et al. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. J Clin Oncol. 2015;33(23):2563–77.
23. Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol. 2015;26(8):1547–73.
24. Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol. 2017;28(10):2340–66.
25. Cheng S, McDonald EJ, Cheung MC, Arciero VS, Qureshi M, Jiang D, et al. Do the American Society of Clinical Oncology value framework and the European Society of Medical Oncology magni-

tude of clinical benefit scale measure the same construct of clinical benefit? J Clin Oncol. 2017;35(24):2764–71.
26. Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, et al. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology position article. J Clin Oncol. 2013;31(29):3711–8.
27. Pallis AG, Ring A, Fortpied C, Penninckx B, Van Nes MC, Wedding U, et al. EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors. Ann Oncol. 2011;22(8):1922–6.
28. Hurria A, Cirrincione CT, Muss HB, Kornblith AB, Barry W, Artz AS, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. J Clin Oncol. 2011;29(10):1290–6.
29. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer. 2009;115(19):4547–53.
30. Soubeyran P, Khaled H, MacKenzie M, Debois M, Fortpied C, Bock R, et al. Diffuse large B-cell and peripheral T-cell non-Hodgkin's lymphoma in the frail elderly: a phase II EORTC trial with a progressive and cautious treatment emphasizing geriatric assessment. J Geriatr Oncol 2011. 2011;2:36–44.
31. de Gramont A, Haller DG, Sargent DJ, Tabernero J, Matheson A, Schilsky RL. Toward efficient trials in colorectal cancer: the ARCAD Clinical Trials Program. J Clin Oncol. 2010;28(4):527–30.
32. Schilsky RL. End points in cancer clinical trials and the drug approval process. Clin Cancer Res. 2002;8(4):935–8.
33. Gill S, Sargent D. End points for adjuvant therapy trials: has the time come to accept disease-free survival as a surrogate end point for overall survival? Oncologist. 2006;11(6):624–9.
34. Buyse M, Molenberghs G, Paoletti X, Oba K, Alonso A, Van der Elst W, et al. Statistical evaluation of surrogate endpoints with examples from cancer clinical trials. Biom J. 2016;58(1):104–32.
35. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350(23):2343–51.
36. Andre T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol. 2015;33:4176–87.
37. Wolmark N, Wieand HS, Kuebler JP, Colangelo L, Smith RE, editors. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: results of NSABP Protocol C-07. In: ASCO annual meeting; 2005.
38. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007;25(16):2198–204.
39. Wolmark N, Wieand S, Kuebler PJ, Colangelo L, O'Connell MJ, Yothers G, editors. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: survival results of NSABP Protocol C-07. In: ASCO annual meeting; 2008.
40. Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? BMC Med. 2017;15(1):134.
41. Sargent DJ, Wieand HS, Haller DG, Gray R, Benedetti JK, Buyse M, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2005;23(34):8664–70.
42. Tang PA, Bentzen SM, Chen EX, Siu LL. Surrogate end points for median overall survival in metastatic colorectal cancer: literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. J Clin Oncol. 2007;25(29):4562–8.
43. Buyse M, Burzykowski T, Carroll K, Michiels S, Sargent DJ, Miller LL, et al. Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol. 2007;25(33):5218–24.
44. Venook AP, Tabernero J. Progression-free survival: helpful biomarker or clinically meaningless end point? J Clin Oncol. 2015;33(1):4–6.
45. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst. 2009;101(23):1642–9.
46. Heinemann V, Stintzing S, Modest DP, Giessen-Jung C, Michl M, Mansmann UR. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). Eur J Cancer. 2015;51(14):1927–36.
47. Piessevaux H, Buyse M, De Roock W, Prenen H, Schlichting M, Van Cutsem E, et al. Radiological tumor size decrease at week 6 is a potent predictor of outcome in chemorefractory metastatic colorectal cancer treated with cetuximab (BOND trial). Ann Oncol. 2009;20(8):1375–82.
48. Modest DP, Laubender RP, Stintzing S, Giessen C, Schulz C, Haas M, et al. Early tumor shrinkage in patients with metastatic colorectal cancer receiving first-line treatment with cetuximab combined with either CAPIRI or CAPOX: an analysis of the German AIO KRK 0104 trial. Acta Oncol. 2013;52(5):956–62.
49. Giessen C, Laubender RP, Fischer von Weikersthal L, Schalhorn A, Modest DP, Stintzing S, et al. Early tumor shrinkage in metastatic colorectal cancer: retrospective analysis from an irinotecan-based randomized first-line trial. Cancer Sci. 2013;104(6):718–24.
50. Suzuki C, Blomqvist L, Sundin A, Jacobsson H, Bystrom P, Berglund A, et al. The initial change in tumor size predicts response and survival in patients with metastatic colorectal cancer treated with combination chemotherapy. Ann Oncol. 2012;23(4):948–54.
51. Liu Y, Litiere S, de Vries EG, Sargent D, Shankar L, Bogaerts J, et al. The role of response evaluation criteria in solid tumour in anticancer treatment evaluation: results of a survey in the oncology community. Eur J Cancer. 2014;50(2):260–6.
52. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50(Suppl 1):122S–50S.
53. Tazdait M, Mezquita L, Lahmar J, Ferrara R, Bidault F, Ammari S, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer. 2018;88:38–47.
54. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013;19(14):3936–43.
55. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143–e52.
56. Becker K, Langer R, Reim D, Novotny A, Meyer zum Buschenfelde C, Engel J, et al. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. Ann Surg. 2011;253(5):934–9.
57. Lorenzen S, Thuss-Patience P, Al-Batran SE, Lordick F, Haller B, Schuster T, et al. Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy. Ann Oncol. 2013;24(8):2068–73.
58. Koh YW, Park YS, Ryu MH, Ryoo BY, Park HJ, Yook JH, et al. Postoperative nodal status and diffuse-type histology are independent prognostic factors in resectable advanced gastric carcinomas after preoperative chemotherapy. Am J Surg Pathol. 2013;37(7):1022–9.

59. McShane LM, Cavenagh MM, Lively TG, Eberhard DA, Bigbee WL, Williams PM, et al. Criteria for the use of omics-based predictors in clinical trials. Nature. 2013;502(7471):317–20.
60. Peppercorn J, Shapira I, Collyar D, Deshields T, Lin N, Krop I, et al. Ethics of mandatory research biopsy for correlative end points within clinical trials in oncology. J Clin Oncol. 2010;28(15):2635–40.
61. Overman MJ, Modak J, Kopetz S, Murthy R, Yao JC, Hicks ME, et al. Use of research biopsies in clinical trials: are risks and benefits adequately discussed? J Clin Oncol. 2013;31(1):17–22.
62. Paoletti X, Ezzalfani M, Le Tourneau C. Statistical controversies in clinical research: requiem for the 3 + 3 design for phase I trials. Ann Oncol. 2015;26(9):1808–12.
63. Braun TM. The current design of oncology phase I clinical trials: progressing from algorithms to statistical models. Chin Clin Oncol. 2014;3(1):2.
64. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst. 2009;101(10):708–20.
65. Hansen AR, Graham DM, Pond GR, Siu LL. Phase 1 trial design: is 3 + 3 the best? Cancer Control. 2014;21(3):200–8.
66. Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst. 1997;89(15):1138–47.
67. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics. 1990;46(1):33–48.
68. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med. 1998;17(10):1103–20.
69. Rogatko A, Babb JS, Tighiouart M, Khuri FR, Hudes G. New paradigm in dose-finding trials: patient-specific dosing and beyond phase I. Clin Cancer Res. 2005;11(15):5342–6.
70. Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I clinical trial design in cancer drug development. J Clin Oncol. 2000;18(3):684–92.
71. Rahma OE, Gammoh E, Simon RM, Khleif SN. Is the "3+3" dose-escalation phase I clinical trial design suitable for therapeutic cancer vaccine development? A recommendation for alternative design. Clin Cancer Res. 2014;20(18):4758–67.
72. Paoletti X, Postel-Vinay S. Phase I-II trial designs: how early should efficacy guide the dose recommendation process? Ann Oncol. 2018;29(3):540–1.
73. Critical role of phase I clinical trials in cancer treatment. American Society of Clinical Oncology. J Clin Oncol. 1997;15(2):853–9.
74. Weber JS, Levit LA, Adamson PC, Bruinooge S, Burris HA, Carducci MA, et al. American Society of Clinical Oncology policy statement update: the critical role of phase I trials in cancer research and treatment. J Clin Oncol. 2015;33(3):278–84.
75. Kairalla JA, Coffey CS, Thomann MA, Muller KE. Adaptive trial designs: a review of barriers and opportunities. Trials. 2012;13:145.
76. Dragalin V, Bornkamp B, Bretz F, Miller F, Padmanabhan SK, Patel N. A simulation study to compare new adaptive dose–ranging designs. Stat Biopharm Res. 2010;2(4):487–512.
77. Liu S, Lee JJ. An overview of the design and conduct of the BATTLE trials. Chin Clin Oncol. 2015;4(3):33.
78. Wathen JK, Thall PF. A simulation study of outcome adaptive randomization in multi-arm clinical trials. Clin Trials. 2017;14(5):432–40.
79. Bowden J, Trippa L. Unbiased estimation for response adaptive clinical trials. Stat Methods Med Res. 2017;26(5):2376–88. Epub 2015 Aug 11.
80. West HJ. Novel precision medicine trial designs: umbrellas and baskets. JAMA Oncol. 2017;3(3):423.
81. Redig AJ, Janne PA. Basket trials and the evolution of clinical trial design in an era of genomic medicine. J Clin Oncol. 2015;33(9):975–7.
82. Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med. 2015;373(8):726–36.
83. Lopez-Chavez A, Thomas A, Rajan A, Raffeld M, Morrow B, Kelly R, et al. Molecular profiling and targeted therapy for advanced thoracic malignancies: a biomarker-derived, multiarm, multihistology phase II basket trial. J Clin Oncol. 2015;33(9):1000–7.
84. Kaplan R. The FOCUS4 design for biomarker stratified trials. Chin Clin Oncol. 2015;4(3):35.
85. Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. Ann Oncol. 2017;28(1):34–43.
86. Cunanan KM, Iasonos A, Shen R, Begg CB, Gonen M. An efficient basket trial design. Stat Med. 2017;36(10):1568–79.
87. Machin D, Campbell MJ, Fayers PM, Pinol A. Sample size tables for clinical studies. Oxford: Blackwell; 1997.
88. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
89. Sheng WQ, Huang D, Ying JM, Lu N, Wu HM, Liu YH, et al. HER2 status in gastric cancers: a retrospective analysis from four Chinese representative clinical centers and assessment of its prognostic significance. Ann Oncol. 2013;24(9):2360–4.
90. Gordon MA, Gundacker HM, Benedetti J, Macdonald JS, Baranda JC, Levin WJ, et al. Assessment of HER2 gene amplification in adenocarcinomas of the stomach or gastroesophageal junction in the INT-0116/SWOG9008 clinical trial. Ann Oncol. 2013;24(7):1754–61.
91. Royston P, Parmar MK, Qian W. Novel designs for multi-arm clinical trials with survival outcomes with an application in ovarian cancer. Stat Med. 2003;22(14):2239–56.
92. Wassmer G, Dragalin V. Designing issues in confirmatory adaptive population enrichment trials. J Biopharm Stat. 2015;25(4):651–69.
93. Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011;30(28):3267–84.
94. Mauer M, Collette L, Bogaerts J, European Organisation for R, Treatment of Cancer Statistics D. Adaptive designs at European Organisation for Research and Treatment of Cancer (EORTC) with a focus on adaptive sample size re-estimation based on interim-effect size. Eur J Cancer. 2012;48(9):1386–91.
95. Burock S, Meunier F, Lacombe D. How can innovative forms of clinical research contribute to deliver affordable cancer care in an evolving health care environment? Eur J Cancer. 2013;49(13):2777–83.
96. Biankin AV, Piantadosi S, Hollingsworth SJ. Patient-centric trials for therapeutic development in precision oncology. Nature. 2015;526(7573):361–70.

Gastrointestinal Cancer Prevention: Diet, Lifestyle, and Therapeutic Prevention

29

Phu N. Tran and Jason A. Zell

Introduction

Gastrointestinal (GI) malignancies are a diverse set of tumors occurring in the GI tract, including cancers of the stomach, esophagus, liver, bile ducts, pancreas, ampulla, small intestine, appendix, large intestine (colon, rectum), and anus. Most GI neoplasms are adenocarcinomas, but other histologic subtypes are commonly encountered, including squamous cell carcinoma, neuroendocrine tumors (NETs) (poorly differentiated NETs as well as well-differentiated carcinoid tumors), gastrointestinal stromal tumors (GIST), sarcomas, lymphomas, and melanoma. Collectively, GI cancers comprise a major global public health burden. The magnitude of the problem is borne out by the numbers: globally, there are approximately 2.5 million cases of GI cancer per year, with gastric cancer, liver cancer, colorectal cancer (CRC), and esophageal cancer representing 4 of the top 10 incident cancers. The same 4 malignancies and pancreas cancer represent 5 of the top 10 causes of cancer mortality, and account for approximately 1.9 million cancer deaths per year [1]. In the United States, CRC has the second highest incidence among cancer affecting both genders, and represents the third most common cancer cause of death [2]. As such, a great deal of importance is placed on prevention efforts aimed at reducing risks attributed to this heterogeneous group of GI cancers. And yet, clear prevention recommendations exist for relatively few of the aforementioned GI malignancies. The focus of this chapter will be to describe cancer prevention efforts of GI malignancies as supported by high-quality evidence. In particular, we focus on diet, lifestyle (physical activity, avoidance of obesity), and therapeutic prevention (chemoprevention) strategies across the spectrum of cancer prevention: from unaffected individuals, to those with pre-neoplastic conditions, to cancer survivors.

In order to describe current strategies for cancer prevention, one must first discuss carcinogenesis (cancer formation) – as cancer prevention strategies and carcinogenesis are intimately linked. Carcinogenesis is well known to occur through the classical steps of initiation, promotion, and progression. Of note, epigenetic influences decrease and histopathological changes increase throughout this process, whereas many cancer prevention strategies (such as smoking cessation) are effective across the spectrum of carcinogenesis. Numerous carcinogenesis models are available for GI cancers, including the best-characterized model of colorectal carcinogenesis. This genetic model for colorectal carcinogenesis was described nearly 30 years ago by Fearon and Vogelstein [3]. In this model (Fig. 29.1a), the transition of histopathologic events from a normal epithelium to dysplasia to early adenoma, late adenoma, frank malignancy, and metastasis is accompanied by a series of genetic and epigenetic events. Lesser known but important carcinogenesis models exist for other tumors within the GI tract (Table 29.1) as well as other non-GI malignancies (most notably, cervical cancer, with CIN I, II, III representing various stages of cervical intraepithelial neoplasia, IEN). The key concept in each of these carcinogenesis models is that intermediate and clinically identifiable histologic changes occur prior to the development of cancer, known collectively as IEN.

Importantly, the carcinogenesis sequence is not predestined or automatic but can be interrupted at different steps of the process. In the words of cancer prevention researcher Dr. Frank Meyskens, "The best treatment of malignant disease is its prevention. The disease to be prevented is carcinogenesis, not cancer" (personal communication, July 1, 2007). As example, colorectal adenomas represent IEN of the colorectum, which are clinically recognized prior to cancer development, and these adenomas can be treated relatively easily for cure. These concepts of carcinogenesis and IEN frame the

P. N. Tran
Department of Hematology/Oncology, Genesis Healthcare System, Genesis Cancer Services, Zanesville, OH, USA

J. A. Zell (✉)
Division of Hematology/Oncology, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, UC Irvine Medical Center, Orange, CA, USA
e-mail: jzell@uci.edu

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_29

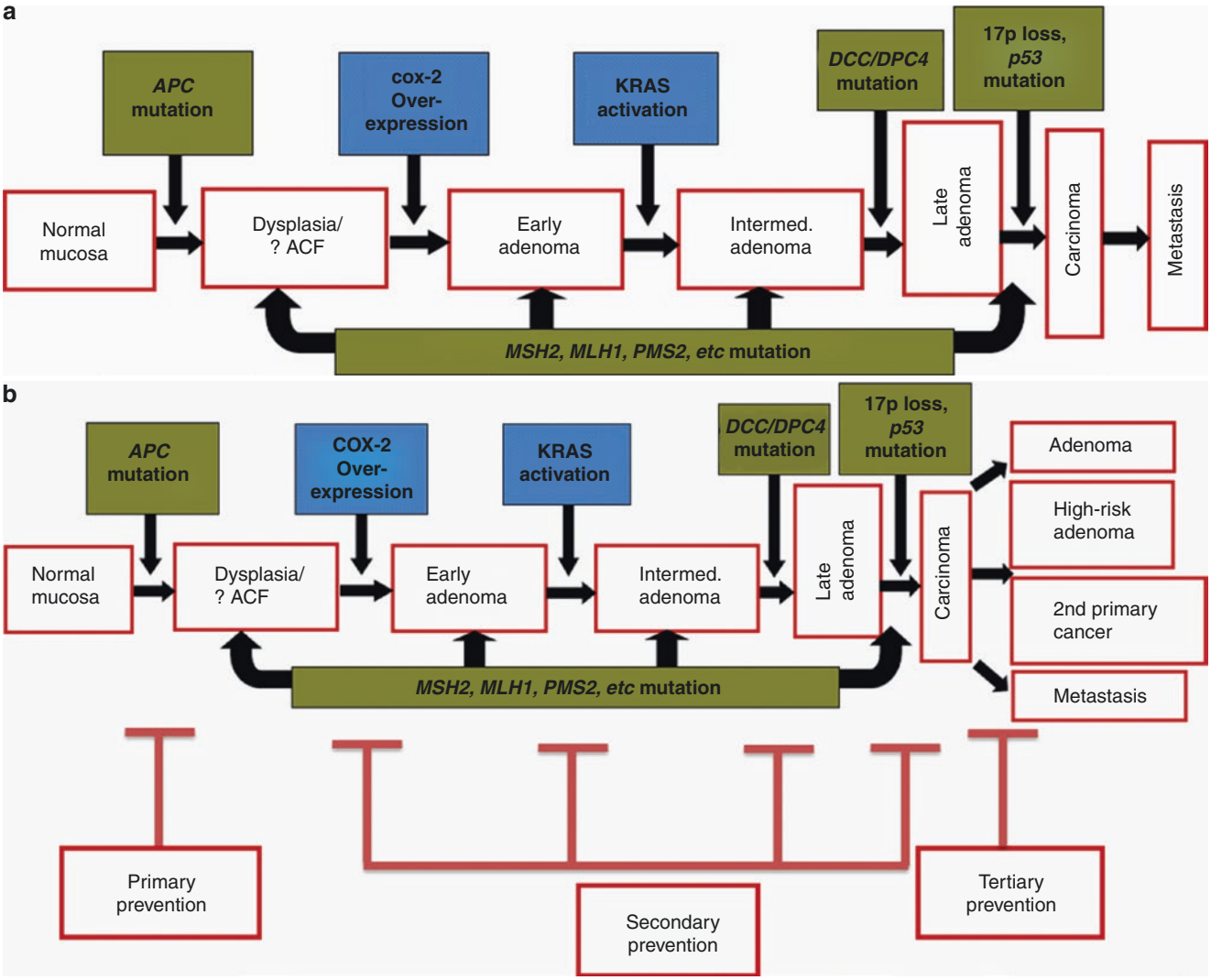


Fig. 29.1 (**a**) Genetic model for colorectal carcinogenesis, adapted from and originally proposed by Fearon and Vogelstein [3]. (**b**) Using the colorectal carcinogenesis model as a scaffold to direct cancer prevention interventions. *ACF* aberrant crypt foci

discussion for the 3 major types of cancer prevention efforts among GI (and non-GI) malignancies: (1) primary prevention, (2) secondary prevention, and (3) tertiary prevention (Fig. 29.1b).

Primary prevention consists of cancer prevention efforts targeting patients without history of cancer, or any pre-neoplastic condition. For example, efforts aimed to reduce cancer risk in the unaffected population fall into this category. Diet modification, physical activity, tobacco awareness, and reduced alcohol intake are common primary prevention recommendations. Examples of primary prevention of GI malignancies include public health recommendations to avoid a diet high in processed meat, in order to reduce the risk of CRC. The advantage of primary prevention, of course, is that such recommendations (when supported by evidence) hold the greatest promise in reducing cancer among average-risk individuals. While primary prevention is the ultimate goal from a public health standpoint, obtaining high-quality data from which to generate evidence-based recommendations is a major challenge. Primary prevention clinical trials are few and far between, as they require enrollment of extremely large numbers of subjects due to the low event rate (i.e., cancer occurrence), over a tremendously long intervention period (decades). Accordingly, primary prevention clinical trials are associated with exorbitant costs, prolonged duration, and are not always feasible.

Secondary prevention entails cancer prevention efforts aimed at patients with pre-neoplastic, clinically identifiable progression, but without frank malignancy (IEN). Identifying and removing colorectal adenomas is an example of secondary prevention. A major advantage is that individuals with IEN can be selected as a high-risk group, and interventions (dietary,

Table 29.1 Premalignant conditions of gastrointestinal cancers and current management guidelines

Cancers	Premalignant conditions	Current practice
Colorectum	Tubular adenoma < Tubulovillous < Villous	Polypectomy and colonoscopy surveillance No polyps or small <10 mm hyperplastic polyps: 10 years 1–2 small (<10 mm) tubular adenomas: 5–10 years 3–10 tubular adenoma: 3 years >10 adenomas: <3 years At least 1 large (>10 mm) adenoma: 3 years One or more villous adenoma: 3 years Adenoma with high-grade dysplasia: 3 years Small (<10 mm) sessile polyp w/o dysplasia: 5 years Large sessile polyp or sessile polyp w dysplasia: 3 years Serrated polyposis syndrome: 1 year
Esophagus	Barrett's esophagus	No dysplasia: EGD surveillance q3–5 years Indeterminate for dysplasia: repeat EGD after 3 months of antireflux therapy Low-grade dysplasia: EGD surveillance q6–12 months versus endoscopic eradication High-grade dysplasia and intramucosal carcinoma: endoscopic eradication
Stomach	Chronic atrophic gastritis, intestinal metaplasia	Test and treat for *H. pylori* EGD surveillance with biopsy mapping every 2–3 years in high-risk individuals
Pancreas	Intraductal papillary mucinous neoplasms (IPMN) Pancreatic intraepithelial neoplasia (PanIn) Mucinous cystic neoplasm (MCN)	Surgery for high-risk IPMN (symptomatic, CBD obstruction, pancreatic ductal dilatation >10 mm, enhancing solid component in the cyst) If main duct IPMN is associated with pancreatic duct dilatation 5-9mm then perform EUS-FNA If main duct IPMN is associated with pancreatic duct dilatation <5 mm then MRCP/CT in 2 yrs For moderate-risk branch duct IPMN (cyst >30 mm, enhancing cyst walls, main pancreatic duct size 5–9 mm, non-enhancing mural nodule, abrupt change in pancreatic duct caliber) perform EUS-FNA If EUS-FNA revealed positive cytology, mural nodules, thickened cyst walls or intraductal mucin then consider resection Clinical management of PanIn or MCN not available
Liver	Cirrhosis	Abdominal US and alpha-fetoprotein every 6 months Transplant eligible if MELD score at least 15
Gallbladder	"Porcelain" gallbladder	Cholecystectomy
Anus	Anal intraepithelial neoplasia (AIN): Low-grade squamous intraepithelial lesion (LSIL): AIN I High-grade squamous intraepithelial lesion (HSIL): AIN II, III, and carcinoma in situ (CIS)	LSIL: Treatment is optional, low risk of progression to malignancy HSIL: Local treatment is required to prevent malignancy

EGD esophagogastroduodenoscopy, *CBD* common bile duct, *EUS-FNA* endoscopic ultrasound fine needle aspiration, *US* ultrasound, *MELD* Model of End-Stage Liver Disease

physical activity, therapeutic prevention) can be tailored to this high-risk group with clear endpoints and shorter follow-up duration than is possible in primary prevention clinical trials.

With advances in screening, early detection, diagnosis, and treatment, more cancer survivors are alive today than at any other time in history. In the United States alone, it is estimated that there were 14.5 million cancer survivors in 2014, and by 2024 it is estimated that the number of cancer survivors will eclipse 19 million [4]. Tertiary prevention focuses on efforts to prevent cancer formation in patients that have previously been treated for cure (i.e., cancer survivors). As will be discussed in this chapter, the past decade has brought about significant progress in tertiary prevention efforts of GI malignancies, particularly CRC. Throughout this chapter, we will identify the available cancer prevention efforts for each GI malignancy based on these major prevention strategies: primary, secondary, and tertiary prevention.

Diet and Prevention of Gastrointestinal Malignancies

Colorectal Cancer

Primary Prevention

Diet is thought to play a major role in CRC pathogenesis and the general consensus is to recommend a diet low in red meat and fat, and high in fruits and vegetables. Many epidemiologic

studies have identified the association between consumption of red meat and processed meats with CRC. A meta-analysis of 10 cohort studies found that the CRC risk associated with consumption of red meat (100 grams per day) or processed meat (50 grams per day) was 17% and 18%, respectively [5]. Several mechanisms have been proposed to explain this association. Cooking red meat at high temperature produces heterocyclic amines and polycyclic aromatic hydrocarbons, which are harmful to cells. Genetic polymorphisms in detoxification pathways for these compounds have been reported to modify the association between red and processed meat intake and CRC risk [6, 7]. In addition, polyamines, which are derived from arginine (a semi-essential amino acid found primarily from dietary meat consumption in non-vegetarians), have been implicated in colorectal carcinogenesis and are found in high quantities in meat, among other foods. For example, preclinical studies demonstrate that dietary arginine increases total and high-grade colon adenoma incidence in $Apc^{Min/+}$ $Nos2^{+/+}$ mice [8, 9]. Heme compounds in red meat increase reactive radical oxygen species while nitrites in smoked, salted, and processed meat products may be converted to carcinogenic N-nitroso compounds in the colon [10]. As a result, the International Agency for Research on Cancer classified red meat as "probably carcinogenic to humans" (Group 2A) and processed meat as "carcinogenic to humans" (Group 1) [11].

Fruits and vegetables have been of great interest to cancer prevention researchers since they contain antioxidants such as vitamins, carotenoids, flavonoids, and fiber. Possible mechanisms include modulation of DNA methylation, protection from and repair of DNA damage, induction of detoxifying phase II enzymes, and promotion of apoptosis [12]. Dietary fiber in fruits and vegetables help decrease insulin-like growth factor 1 (IGF-1) activity and inflammatory cytokines, alter gut flora, and exert local effects on the colonic mucosa such as diluting carcinogens and biliary acids [13]. In contrast to the positive results from older case-control studies, most recent cohort studies report weak associations between high intake of fruits and vegetables and lower risk of CRC. A pooled analysis of 14 cohort studies ($n > 750{,}000$) found that intake of 800 g fruit and vegetables daily decreases risk for distal colon cancer (RR 0.74) but not for proximal cancer (RR 1.02), compared to intake of less than 200 g per day [14]. A subsequent meta-analysis of 19 cohort studies confirmed the weak association and suggested little additional benefits associated with higher fruit intake of more than 100 g/day [15]. Taken together, increasing the consumption of fruits and vegetables beyond the levels associated with a balanced diet appears to offer little additional cancer preventive benefit.

Secondary Prevention

A high fiber diet including diets high in fruits and vegetables does not appear to affect the adenoma recurrence rate among adenoma patients. Data from the Polyp Prevention Trial showed that large amounts of fruits and vegetables (as well as high fiber and low fat) failed to reduce the risk of recurrent adenoma when compared to a usual American diet that included at least 200–400 g/day of fruits and vegetables – even at 8-year follow-up [16, 17]. Similarly, the Phase III Wheat Bran Fiber trial demonstrated no difference in adenoma recurrence rate in patients who took high-fiber supplements (13.5 g/day) versus low intake (2.0 g/day) [18]. However, a very high dietary consumption of beans has been associated with lower adenoma recurrence rate in the Polyp Prevention Trial. Individuals in the highest quartile of dry bean intake compared with those in the lowest had a 65% reduction in the recurrence of advanced adenomas (OR = 0.35) [19]. The total intake of dry beans in the intervention group (high intake of low-fat, high-fiber, high-fruit, and vegetable dietary) was 39 g/d, which is considerably higher than the average intake for US men (21 g/day) and women (13 g/day). Perhaps certain flavonoid subtypes in beans contribute to the observed beneficial effects on adenoma prevention. Sub-analysis of dietary data from the Polyp Prevention Trial found that high intake of flavonols and isoflavonoids, not total flavonoid, was associated with a lower risk of adenoma recurrence (4th versus 1st quartile group in bean intake) [20]. Flavonols are commonly found in beans, onions, apples, and tea. In contrast, high intake of flavanones was associated with higher risk of adenoma recurrence.

Tertiary Prevention

There is robust observational evidence on colon cancer recurrence risk in survivors with persistently high red meat intake. Observational data from the National Clinical Trials Network (NCTN) trial C89803, an adjuvant chemotherapy study of stage III colon cancer patients, revealed that colon cancer survivors in the highest Western dietary pattern (characterized by higher intakes of red and processed meats, sweets and desserts, French fries, and refined grains) after diagnosis had a 3-fold increased risk of recurrence and a 2.3-fold increased risk of all-cause mortality compared with patients in the lowest quintile [21, 22]. Surprisingly, a prudent diet (high in legumes, fish, and vegetables) was not associated with mortality outcomes in this study. Consumption of more than 4.1 servings per week of red meat after colon cancer diagnosis was associated with 79% increased risk of CRC mortality according to the Cancer Prevention Study II Nutrition Cohort study [23]. Processed meat consumption was associated with higher cancer recurrence rate and inferior overall survival (OS) to greater extent in the colon than rectum. In a cohort study of 529 newly diagnosed Stage I to III CRC patients in Newfoundland, high processed-meat consumption was associated with worse disease-free survival (DFS) in patients with colon cancer (HR 2.29) but not rectal cancer (HR 0.97) [24]. No associations were observed with the prudent vegetable or high-sugar diet patterns and DFS. In a population-based analysis of CRC patients enrolled in an epidemiologic study at the

University of California Irvine, high overall meat consumption of all types was associated with increased risk of death among familial (but not sporadic) CRC patients, suggesting complex relationships between genetics and diet [25]. In contrast, pre-diagnosis meat consumption was not associated with CRC-specific mortality among 704 CRC patients in the California Teachers Study. However, regular nonsteroidal anti-inflammatory drug (NSAID) use (1–3 times/wk, 4–6 times/wk, daily) versus none was associated with decreased CRC-specific mortality among patients in the lowest meat consumption tertile (HR 0.22), but not among patients in the higher meat intake tertiles [26]. It is postulated that high polyamine intake from meat consumption negates the protective effects of NSAIDs, which are known to regulate cellular polyamine pools by inducing spermine acetyltransferase and resultant cellular polyamine export [26].

High glycemic load and total carbohydrate intake may be associated with colon cancer recurrence and mortality. Colon cancer survivors in the highest quintile of carbohydrate intake group were reported to have a 2-fold increased risk of disease recurrence and all-cause mortality compared with individuals in the lowest quintile [27]. Similarly, consumption of 2 sugar-sweetened beverages per day after colon cancer diagnosis had a 75% increased risk of recurrence compared with individuals who consumed 2 per month [28].

Emerging data suggest that coffee consumption may lower the risk of recurrence and colon cancer-specific mortality among colon cancer patients. Coffee consumption has been associated with decreased risk of type 2 diabetes mellitus (DM), lower plasma C-peptide, and increased plasma adiponectin, an endogenous insulin sensitizer. Based on data emanating from C89803, survivors of Stage III colon cancer who consumed 4 cups of coffee per day had lower risk of colon cancer recurrence than never drinkers (HR 0.58) and abstainers (HR 0.48) [29]. The benefits appear to be proportional to the amount of coffee intake. There were no observed benefits for non-herbal tea or decaffeinated coffee.

Non-colorectal Gastrointestinal Tumors

The association between dietary intake and other GI cancers is less well studied and mostly focused on primary prevention. Diet is thought to be important in the etiology of gastric cancer, and dietary changes are implicated in the recent decline in stomach cancer incidence in the developed world. Data from case-control studies suggest that risk is increased by high intakes of traditionally preserved foods, especially salty meats and pickles, while risk is decreased by high intakes of fruits and vegetables [30]. The high intake of salted and pickled vegetables/foods is associated with 50% higher risk of gastric cancer in Korea and China [31].

Prospective studies report mixed results regarding the protective effect of fruits and vegetables for gastric cancer [32–34]. Despite the anticancer effect of green tea in preclinical studies, most prospective observational studies report no association of green tea consumption and reduced gastric cancer risk [35]. Well-designed studies are needed to examine if the association between diet and gastric cancer is confounded by *Helicobacter pylori*, among other factors. Similar to gastric cancer, foods containing N-nitroso compounds have long been implicated in the development of esophageal cancer. Aflatoxin from food contaminated with endemic fungi in grains and peanuts may exert their mutagenic potential by reducing nitrates to nitroso compounds [36]. Frequent intake of hot food may be associated with increased risk of esophageal cancer, possibly by causing chronic mucosal injury [37]. Multiple studies have consistently observed an inverse relationship between high fruit and vegetable intake and development of esophageal cancer [30, 38]. For hepatocellular carcinoma, excess alcohol intake remains the most important etiology in the Western society, probably via the development of cirrhosis. Exposure to aflatoxin is an important risk factor among people in developing countries, especially in individuals with chronic viral hepatitis [39]. There is inconclusive evidence regarding the association of fiber, fruits, and vegetable with HCC. Interestingly, coffee has been consistently shown to be associated with lower HCC risk. Three recent meta-analyses comprising thousands of patients suggested that coffee intake is inversely proportional to HCC risk [40–42]. New observational data suggest that coffee may help prevent HCC by reducing the risk of cirrhosis in a dose-response manner. In a meta-analysis involving more than 400,000 participants, daily intake of 2 cups of coffee was associated with reduction in all-cause cirrhosis and alcoholic cirrhosis by 44% and 38%, respectively [43]. Regarding pancreatic cancer, a World Cancer Research Fund panel concluded that there is limited evidence to suggest that intake of food high in red, processed meat, or saturated fat increased pancreatic cancer risk. Although there is no clear association between moderate alcohol intake and pancreatic cancer, heavy drinkers (more than 3 drinks per day) have a significant increased risk [44].

Lifestyle Factors Related to Prevention of Gastrointestinal Malignancies

Physical Activity

Colorectal Cancer

Primary Prevention

Physical inactivity has major public health implications because it is the second leading cause of preventable death in the United States (after smoking). About 37.7% of the US population is not active enough for health benefits and an additional 14.2% does not exercise more than 10 minutes each

week on average [45]. Physical activity is inversely related to CRC risk (RR 0.76) according to a meta-analysis of 52 studies [46]. Further meta-analyses estimated a 15% risk reduction of colon polyps and 27% risk reduction of colon cancer due to physical activity [47, 48]. The possible protective mechanisms of exercise include improving water intake, reducing IGF-1, and inflammatory markers such as prostaglandins, and altering bile acid secretion and gut flora [49, 50]. Although the optimal intensity, duration, and frequency of physical activity required to reduce cancer risk are unknown, the American Cancer Society recommends about 30 minutes of moderate to strenuous exercise at least 5 days a week [51].

Secondary Prevention

There are few studies examining the role of physical activity in secondary prevention of colon cancer. A pooled analysis from 2 randomized trials including 1,730 participants concluded that sedentary behavior is associated with higher risk of colorectal adenoma recurrence among men but not women. Compared to the lowest quartile of sedentary time, the odds ratio for the second, third, and fourth quartiles among men were 1.23, 1.41, and 1.47, respectively [52]. The Polyp Prevention Trial found no significant associations between moderate, vigorous, or total physical activity at the start of the trial and overall polyp recurrence in either men or women [53]. Consistent vigorous activity was also not significantly associated with either advanced or multiple polyps, nor with polyp recurrence at any specific anatomical location in the large bowel.

Tertiary Prevention

In general, cancer survivors rarely return to their pre-diagnosis levels of activity after treatment [54, 55]. The combined detrimental effects of cancer, treatment, and recovery hinder survivors from increasing physical activity. Numerous studies have suggested that exercise improves quality of life in cancer survivors but few studies have examined the role of exercise on disease-free survival and cancer-specific mortality. Among colon cancer patients, it is striking to note that even a small amount of physical activity may affect disease outcome and recurrence. In the Melbourne Collaborative Cohort Study comprising of 526 CRC patients, the investigators found that regular physical activity, even as little as once per week, was associated with an absolute improvement of 14% in overall survival (OS) and 12% in disease-specific survival at 5 years compared with no regular activity. The benefits were seen mainly in Stage II–III colon cancer survivors with a 39% reduction in overall mortality and 51% reduction in disease-specific mortality. No effect on survival was noted for the rectal cancer subgroup [56]. High-level activity is associated with better outcomes than low-level activity according to observation data from the Nurses' Health Study (NHS) cohort. In this study CRC-specific mortality (HR 0.39) and overall mortality (HR 0.43) were lower in women who engaged in activity at least 18 MET (metabolic equivalent of task)-hours per week compared with those with 3 MET-hours/week [57]. Similarly, men who engaged in 27 MET-hours/week of physical activity had lower CRC-specific mortality (HR 0.47) than those who did less than 3 MET-hours/week. The benefit of physical activity was seen regardless of age, stage, body mass index (BMI), tumor location, and pre-diagnosis physical activity [58]. Categories of MET-hour/week were predefined as less than 3, 3–8.9, 9–17.9, and 18 or more, to correspond to the equivalent of less than 1, 1 to less than 3, 3 to less than 6, and 6 or more hours per week of walking at an average pace [57]. Physical activity may provide additional benefit in recurrence and survival outcomes above the benefit seen with surgery and adjuvant chemotherapy. In a prospective observational study of 832 stage III colon cancer patients receiving adjuvant chemotherapy from the National Clinical Trials Network (NCTN) C89803 trial, patients who exercised 18–26.9 MET-hours/week and >27 MET-hours/week had improved DFS with HRs 0.51 and 0.55, respectively, relative to those who exercised <3 MET-hours/week [59]. This study also suggested that the protective effect of physical activity can be seen at 6 MET-hours/week.

A link has been proposed between specific molecular markers and benefits from physical activity. Patients with tumors harboring p27 loss and WNT-CTNNB1 who engaged in 18 MET-hour/week of physical activity were found to have 67% risk reduction in cancer-specific mortality [60, 61]. Additionally, patients with prostaglandin-endoperoxide synthase 2 (PTGS2)-positive tumors who engaged in the highest quartile of physical activity had an 82% lower risk of colorectal cancer-specific mortality compared with the least-active individuals [62]. There was no association between physical activity after diagnosis and survival in those with PTGS2-negative tumors. These studies shed light on the positive impact of physical activity on risk of CRC progression and recurrence, partly by modulating energy metabolism and inflammatory signals.

While observational studies establish a strong association between physical activity and improved outcome among colon cancer survivors, a randomized controlled trial is needed to determine whether the association is causal. To this end, the Colon Health and Life-Long Exercise Change (CHALLENGE) trial undertaken by the National Cancer Institute of Canada was designed to determine the effects of a structured physical activity intervention on outcomes for survivors of high-risk stage II or III colon cancer who have completed adjuvant therapy within the previous 2–6 months [63]**.** The study is currently recruiting patients (NCT00819208).

Non-colorectal Gastrointestinal Cancers

In general, there is a trend for lower risk of non-colorectal GI cancers in active individuals even though the published evidence is not conclusive. Physical activity likely reduces GI cancer risk through its beneficial effect on insulin sensitivity,

inflammation, and obesity [64]. Most studies observed an inverse relationship between physical activity and lower risk of esophageal adenocarcinoma [65, 66]. The benefit of physical activity seen in esophageal adenocarcinoma was mainly observed in obese individuals. No significant relationship with physical activity was observed for esophageal squamous cell carcinoma [66]. The association between physical activity and gastric cancer remains unsettled due to heterogeneous study designs and findings. Some case-control and cohort studies found a significant inverse relationship of physical activity to gastric cancer, with relative risk estimates ranging from 0.32 to 0.79; whereas others did not [66]. Further well-designed prospective studies and meta-analyses are required to answer this question. Most studies consistently reported a decreased risk of liver cancer with higher levels of physical activity, including total activity, leisure time activity, walking, and vigorous activity [67]. However, because different types of activity were measured and a variety of measures were used to collect the data, no meta-analyses could be conducted. While most studies observed the increased risk of pancreatic cancer in obese individuals, evidence supporting benefits of physical activity is mixed. Two US cohort studies comprising 47,000 men and 117,000 women concluded that moderate activity (<6 METs) was associated with decreased risk of pancreatic cancer, especially among those who are overweight with BMI > 25 kg/m^2 [68]. Data from a prospective cohort study of 80,000 people in Japan suggest that physical activity is associated with lower risk of pancreatic, liver, and colon cancers even in non-obese individuals [69]. In contrast, a US cohort study of 146,000 individuals reported no difference in pancreatic cancer incidence rates between men and women who were most active (>31 MET hours per week) at baseline compared to those who reported no recreational physical activity [70].

Control of Obesity

Colorectal Cancer

Primary Prevention

Obesity is a major health epidemic with increasing prevalence of 15% in 1980 to 35% in 2005 in the United States. It is estimated that the relative risk of CRC in obese individuals is modest (RR 1.09) [71]. Growing evidence points to hyperinsulinemia as a direct link from obesity to CRC. For instance, high glucose, c-peptide (a marker of insulin production), and high IGF levels are associated with increased risk (Fig. 29.2) [71]. Obese men with BMI more than 30 had an 80% increased risk of CRC relative to men with normal BMI [72]. Additionally, weight gain of 21 kg in men age 30 to 50 was associated with 80% and 50% increased risks of colon and rectal cancers, respectively. A meta-analysis comprised of 9 million individuals from 54 studies concluded that both general and central obesity increase CRC risk in men and women [73]. The effect of weight loss on CRC was reported in a population-based study of more than 65,000 adults in Austria. In this study, weight loss (>0.10 kg/m^2/year) was associated with 50% colon cancer risk reduction in men [74]. Bariatric surgery appears to reduce CRC risk (RR 0.32) and other obesity-related cancers in morbidly obese individuals [75].

Secondary Prevention

Obesity is associated with an increased adenoma recurrence rate. A pooled analysis from 2 randomized control trials (n = 2,465) found that BMI > 30 was associated with increased odds of having recurrent adenoma in men (OR 1.36) but not women (OR 0.90) [76]. The odds of adenoma recurrence increased drastically among obese individuals with family history of colorectal cancer (OR 2.25). A Korean cohort study also found significant associations between recurrent adenoma and metabolic syndrome (HR 1.33) in men [77]. A case-control study in Italy identified BMI > 30 as independent predictors of synchronous polyps (OR 2.2) [78]. This study also reported higher cancer recurrence rate in obese patients with stage II CRC with respect to the non-obese (p = 0.05). However, this study did not perform gender-specific analysis so it is unclear if obese women had higher recurrence rates. Despite the adverse consequence of obesity on adenoma recurrent rate, there is no convincing evidence suggesting that weight loss alone is a sufficient secondary prevention. Retrospective analysis of a Japanese cohort estimated that loss of 5% or more body weight among Japanese patients over 1 year was associated with reduction in adenoma recurrence (OR 0.47) [79]. The study's limitations included its retrospective nature and short (1-year) follow-up duration. The prospective controlled Polyp Prevention Trial found no association between weight change and polyp recurrence (all weight changes, RR = 1.00; weight loss only, RR = 1.00; and weight gain only, RR = 1.00) [80].

Tertiary Prevention

There is convincing evidence for the adverse effect of obesity in cancer survivors. In a prospective study of more than 900,000 US cancer survivors, there was increased death from all cancers and obesity-related cancers due to obesity. The study estimated that overweight and obesity in the US could account for 14% of all deaths from cancer in men and 20% of those in women [81]. Moreover, obese women with Stage II–III colon cancer at baseline had inferior survival and higher recurrence rates despite absence of chemotherapy-related toxicity, when compared with women of normal weight [82]. The evidence for the positive impact of weight loss on survival and recurrence in cancer survivors is less conclusive. An Australian study concluded that increasing body fat and waist circumference decrease cancer-specific survival and that weight loss by increasing activity improve overall and CRC-specific survival [56]. In a cohort of 21,707 postmenopausal female cancer survivors,

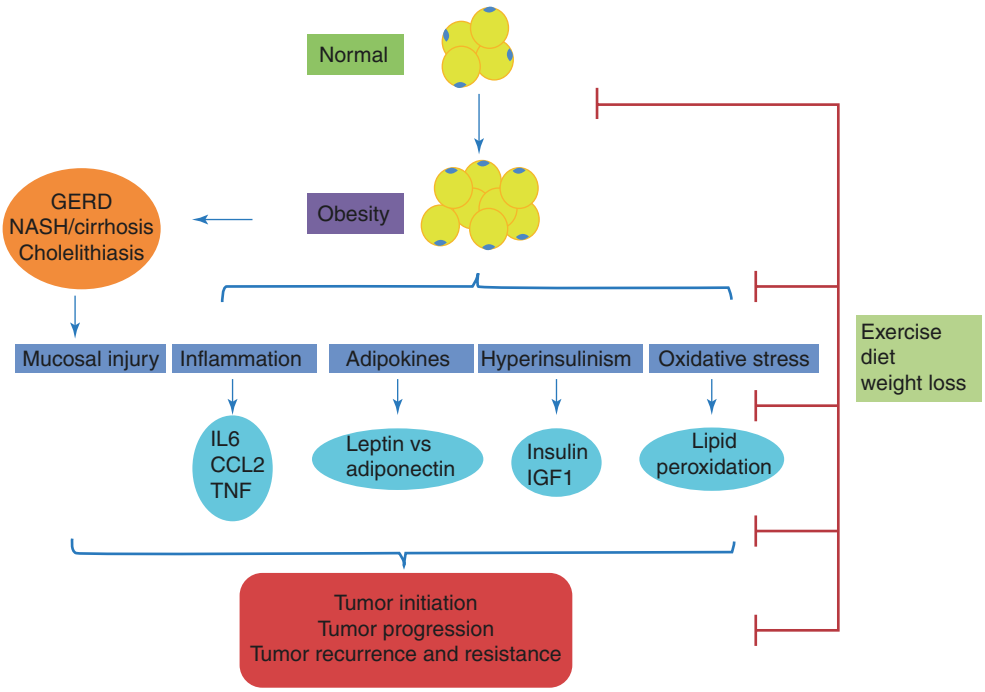


Fig. 29.2 Mechanisms of gastrointestinal carcinogenesis due to obesity and potential interventions. *GERD* gastroesophageal reflux disease, *NASH* nonalcoholic steatohepatitis, *IL6* interleukin 6, *CCL2* C-C motif chemokine ligand 2, *TNF* tumor necrosis factor, *IGF1* insulin-like growth factor 1

women who experienced intentional weight loss >20 pounds had lower incidence rates of 11% for any cancer, 9% for colon cancer, and 14% for all obesity-related cancer after adjusting for other confounders [83]. In contrast, a prospective, observational study of 1,053 patients who had stage III colon cancer, found no association between intentional weight loss with disease-free survival time or overall mortality [84]. In summary, obesity appears to have detrimental effects on colon cancer survival and recurrence, but it is less clear if weight reduction alone improves outcomes.

Non-colorectal Gastrointestinal Cancers

Obesity accounts for 20% of all cancer cases and a 5 kg/m^2 increase in BMI is strongly associated with esophageal (RR 1.51), gallbladder (RR 1.59), pancreatic (RR 1.12), colorectal (RR 1.09), and liver cancer (RR 1.07) [85]. The pathophysiology of obesity is complex and likely contributes to different GI malignancies by different mechanisms (Fig. 29.2) [71]. The high insulin state and chronic inflammation from obesity likely drive colon and pancreatic cancers. Obesity contributes to liver cancer development indirectly by causing nonalcoholic steatohepatitis (NASH) and eventual liver cirrhosis. Esophageal adenocarcinoma is caused by reflux esophagitis and gallbladder cancer is caused by chronic irritation from secretion-gallstones, both of which are related to obesity. Obese individuals have about a 2.5-fold risk of Barrett's esophagus, which is a precursor lesion to esophageal adenocarcinoma [86]. Obesity-related markers, including leptin and inflammatory mediators, are correlated to increased risk of esophageal adenocarcinoma (EA) progression from Barrett's esophagus, whereas adiponectin had a nonlinear inverse association with risk of EA [87]. There is no relationship between obesity and esophageal squamous cell carcinoma, which is associated with tobacco, alcohol, human papillomavirus (HPV), and achalasia. For stomach cancer, recent meta-analyses support an increased risk of proximal (cardia) gastric cancer in relation to body fatness, making the evidence as "suggestive." For distal (non-cardia) gastric cancer the level of evidence regarding obesity and cancer risk remains inconclusive [88]. Weight loss appears to benefit women with obesity-related cancers more than men. For instance, women who experienced intentional weight loss >20 pounds had 14% lower incidence for obesity-related cancer after adjusting for other confounders [83]. Perhaps the most convincing evidence that establishes the role of weight loss in decreasing overall cancer incidence comes from a prospective interventional trial called the Swedish Obese Subjects. In this trial, obese women who underwent bariatric surgery had lower overall cancer incidence (HR 0.67) than the control group who received conventional care. No observed difference in cancer incidence was seen in men (HR 0.97). The lack of benefits of bariatric surgery in men in this study may be due to smaller sample size (1,180 men versus 2,867 women). In addition, weight loss appears to have the largest impact on breast and endometrial cancers, which likely drive the cancer-reduction benefits seen in women [75]. A retrospective observational study identified an association between bariatric surgery and lower prevalence of liver cancer in academic institutions. Individuals with a history of bariatric surgery had a 61% lower prevalence of liver cancer compared to those without, even after adjusting for sex, race, and ethnicity [89].

Therapeutic Prevention

Colorectal Cancer

The bulk of clinical trials evidence supporting therapeutic prevention of GI malignancies involves prevention of CRC (Table 29.2). Beyond the scope of this chapter is CRC screening, including colonoscopy screening – which is unique among screening paradigms as detection and removal of preneoplastic lesions can be accomplished simultaneously. Prior to discussing therapeutic prevention of CRC, it must be acknowledged that the declines in US CRC incidence and mortality rates over the past few decades have been attributed largely to CRC screening programs as well as advances

Table 29.2 Select colorectal cancer chemoprevention studies

Author	Study setting	Study design	Number of patients	Intervention	Primary outcome
Aspirin/NSAIDs					
Steinbach, 2000	Secondary, FAP patients	Randomized, double-blind	77	Celecoxib	Decreased mean number of polyps by 28%
Nugent, 1993	Secondary, FAP patients	Randomized	24	Sulindac	Decreased duodenal and rectal polyposis
Higuchi, 2003	Secondary, FAP patients	Randomized, double-blind	21	Rofecoxib	Compared to placebo, rofecoxib arm had decreased polyp number (9.9%) and size (−16.2% versus 1.5%) at 9 months
Bertagnolli, 2006	Secondary	Randomized, double-blind	2035	Celecoxib	Reduced risk of recurrent adenoma vs. placebo (risk ratio 0.67); increased cardiovascular toxicity at 1 year
Chan, 2007	Primary	Population-based	130,000	Aspirin	Reduced incidence of CRC (RR 0.64) among COX-high individuals
Benamouzig, 2003	Secondary	Randomized, double-blind	272	Aspirin	Reduced risk for recurrent adenomas found at colonoscopy 1 year after treatment (RR 0.73).
Sandler, 2003	Secondary	Randomized, double-blind	517	Aspirin	Reduced risk of recurrent adenoma RR 0.65 at 12.8 months follow-up
Ishikawa, 2014	Tertiary	Randomized, double-blind	311	Aspirin	Lower risk of cancer recurrence in non-smokers taking aspirin (OR 0.37). Higher risk of recurrence with smoker taking aspirin (OR 3.44) in Asians
Chan, 2009	Tertiary	Randomized, double-blind	1279	Aspirin	Reduced CRC mortality in patients with COX2 high tumors (HR 0.39) but not COX2 low tumors (HR 1.22) at 11.8-year follow-up
Liao, 2012	Tertiary	Retrospective observation	964	Aspirin	Improved CRC survival (HR 0.18) and OS (HR 0.54) among patients with *PIK3CA* mutation
Kothari, 2015	Tertiary	Prospective observation	1487	Aspirin	No improvement in OS (HR 0.96) or CRC survival (HR 0.60)
Zell, 2009	Tertiary	Population-based, prospective	621	NSAIDs	Improved OS (HR, 0.55) and CRC-specific survival (HR 0.40) with NSAID intake among women
Ca^{2+} and vitamin D					
Wactawski-Wende, 2006	Primary	Randomized, double-blind	36,282	Ca^{2+}, Vitamin D	Ca^{2+}/Vitamin D had no effect on the incidence of CRC among postmenopausal women at 7 years
Baron, 1999	Secondary	Randomized, double-blind	930	Calcium	Decreased risk of adenoma recurrence (HR 0.85)
Baron, 2015	Secondary	Randomized, double-blind	2259	Ca^{2+}, Vitamin D, or both	No effect of intakes of vitamin D_3 calcium, or both on recurrent adenomas at 3–5 years
Statins					
Poynter, 2005	Primary	Population- based, retrospective	3968	Statins	Associated with decreased colorectal cancer (odds ratio, 0.50)
Coogan, 2006	Primary	Population- based, case control	3618	Statins	Associated with no reduced overall risk of CRC (OR 0.92) but reduced risk of Stage IV CRC (OR 0.49)
Lee, 2011	Primary	Population- based, prospective	131,922	Statins	Associated with reduced risk for rectal cancer (RR 0.59) but not colon cancer (RR 0.99)
Metformin					
Hosono, 2010	Secondary, Biomarker	Randomized controlled	26	Metformin	At 1-month follow-up metformin group had decreased rectal aberrant crypt foci vs. control
Zell, 2014	Secondary, Biomarker	Randomized controlled	45	Metformin	Twelve weeks of PO metformin did not reduce pS6 level (surrogate marker of PI3K pathway) in rectal mucosa
Polyamine inhibitors					
Meyskens, 2008	Secondary	Randomized controlled	375	DFMO and Sulindac	DFMO/Sulindac-treated arm had lower adenoma recurrence (12.3%) vs. placebo (41.1%); risk ratio 0.30

NSAIDs nonsteroidal anti-inflammatory drugs, *FAP* familial adenomatous polyposis, *CRC* colorectal cancer

in treatment. As discussed, the well-characterized genetic model of colorectal carcinogenesis has been used successfully as a framework for designing high-quality therapeutic prevention clinical trials. As with therapeutic cancer clinical trials development, a clear balance of safety must be measured against clinical benefit, in a risk-stratified manner. For therapeutic prevention trials, however, the risk threshold is necessarily quite low – since the population at risk is typically without malignancy.

Aspirin and Nonsteroidal Anti-inflammatory Drugs

Multiple lines of evidence from experimental [90–95], epidemiologic [96–100], and clinical trials research [101–105] have implicated aspirin and NSAIDs in the primary prevention of CRC. Aspirin is an anti-inflammatory agent, involved in prostaglandins inhibition [106]. Cyclooxygenase (COX)-2 selective and non-selective NSAIDs similarly reduce carcinogenesis within the colon through inhibition of prostaglandin synthesis (Fig. 29.3) [107]. In patients with familial adenomatous polyposis (FAP), one of the major dominantly inherited genetic colorectal cancer syndromes, NSAIDs clearly reduce adenoma formation [102, 104]. Furthermore, aspirin has been shown in clinical trials to reduce the risk of recurrent adenomas by 25–30% among adenoma patients (secondary prevention) [108] and CRC survivors (tertiary prevention) [109]. Clinical trials of various NSAIDs have been shown to result in a 40–50% reduction of recurrent adenomas (secondary prevention), however, at the cost of cardiovascular toxicity [110]. As such, NSAIDs are not recommended for primary prevention of CRC by the United States Preventive Services Task Force (USPSTF) [111]. Multiple observational studies in CRC survivors have contributed to our understanding of the roles of aspirin and prevention of CRC progression. Among CRC survivors, regular aspirin and NSAIDs use have been associated with improved overall survival and cancer-specific survival [112, 113]. Subsequent studies of CRC survivors reveal important tumor characteristics that exhibit specificity for the association of aspirin with improved outcomes. In one study, patients with CRC tumors expressing COX-2 (which includes 67% of all CRC patients), regular aspirin use was associated with mortality risk reduction [114]. However, aspirin was associated with no risk reduction among CRC patients having tumors that lack COX-2 expression. Similarly, investigators have examined PIK3CA mutations in tumors from CRC patients, due to well-described roles of the phosphatidylinositol cascade in colorectal carcinogenesis. Initial reports revealed a strong association of regular aspirin use and tumor PIK3CA mutation with prolonged overall survival and CRC-specific survival [115]. Individuals lacking PIK3CA mutation were observed to have no survival benefits of regular aspirin use. Other investigators reported similar findings [116], while the findings from a third study failed to confirm these results [117]. Of note, the "dissenting" report had low statistical power. Finally, the benefit of aspirin in tertiary colorectal prevention was observed mostly in non-smokers [118, 119]. Aspirin intake among smokers was actually associated with higher cancer recurrence rate. Given the higher risk threshold for cancer survivors, a phase III clinical trial of the

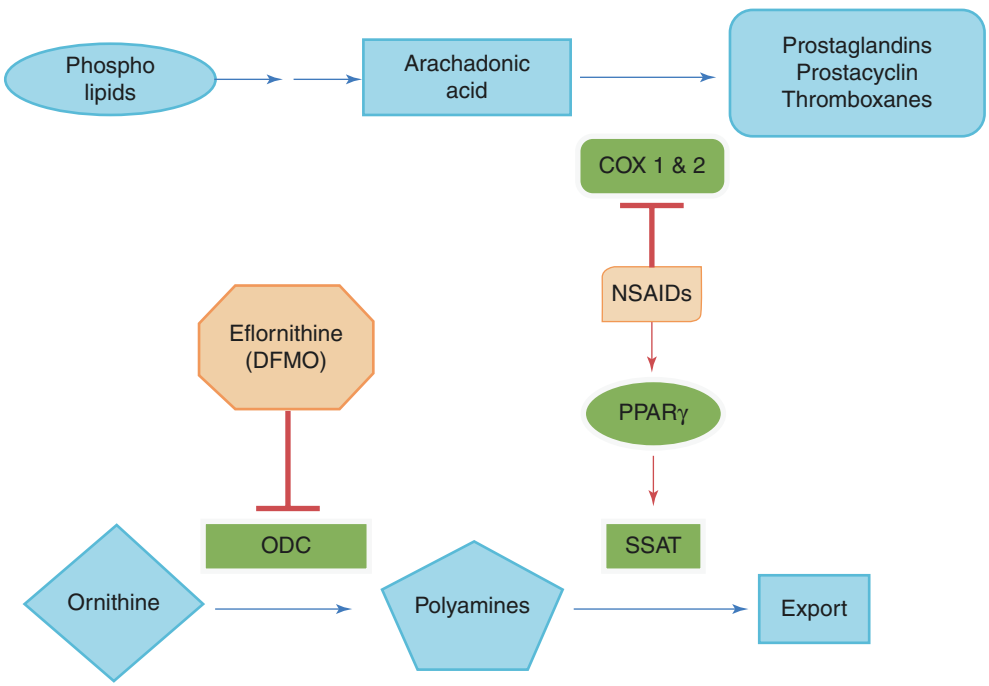


Fig. 29.3 Mechanisms of nonsteroidal anti-inflammatory drugs (NSAIDs) and eflornithine in relation to the arachadonic pathway and polyamine metabolism. NSAIDs inhibit cyclooxygenases (COX 1&2), which are central to metabolism of arachidonic acid into various prostanoids such as thromboxane and prostaglandins. NSAIDs stimulate peroxisome proliferator-activated receptor gamma (PPAR-γ[gamma]). PPAR-γ(gamma) in turn upregulates spermidine/spermine-N^1-acetyltransferase (SSAT). SSAT is involved in polyamine catabolism. Eflornithine decreases polyamine level by inhibiting ornithine decarboxylase (ODC)

COX-2 selective NSAID celecoxib in stage III colon cancer patients was launched through the US NCTN in 2010. This clinical trial completed accrual in Fall 2015 (NCT01150045), with results anticipated in the next couple of years.

Calcium/Vitamin D

Multiple preclinical studies have established the antiproliferative mechanisms of calcium and vitamin D. Calcium is an essential micronutrient that serves as a second messenger for many cellular pathways. Putative biological activities related to the apparently protective effects of calcium in the colon include binding of bile acids, decreasing cytotoxicity of fecal water, inhibition of cellular proliferation, and induction of apoptosis [120]. Vitamin D promotes cell cycle arrest by partly suppressing cyclin D, stimulates cell differentiation via a pathway involving β(beta)-catenin, and stimulates apoptosis by upregulating pro-apoptotic proteins (BAK, BAX) and downregulating anti-apoptotic signals (BCL-2) [120, 121]. Numerous observational studies report associations between regular calcium and CRC risk [122–124]. Reported associations for vitamin D intake and reduced CRC incidence are inconsistent [125–127]. Reports of any benefits of calcium and vitamin D supplements on secondary prevention of CRC are mixed. Calcium supplementation has been proven to decrease recurrent adenomas by 25–30% in adenoma patients [128] and also in an NCTN trial of cancer survivors [129]. In contrast, a recent prospective randomized trial found no secondary preventive benefit for daily supplementation with vitamin D, calcium, or both after removal of colorectal adenomas over a period of 3–5 years [130]. While calcium supplementation has been proven to reduce colorectal adenomas in the clinical trial setting, effects on CRC risk are lacking. The Women's Health Initiative (WHI) study, a randomized controlled trial of more than 36,000 women given calcium and vitamin D versus placebos for 7 years, revealed no effect on CRC risk among postmenopausal women [131]. Recently, vitamin D has reemerged as a potential chemopreventive agent for CRC. A recent observational study of stage IV CRC patients revealed associations of vitamin D with prolonged survival outcomes [132]. Certainly, calcium and vitamin D meet the criteria for safety in the setting of CRC prevention. However, since the reported cancer-preventive effects of calcium and vitamin D are modest in comparison with other agents (such as NSAIDs and the polyamine inhibitors), the role of calcium and vitamin D in CRC prevention is currently undefined.

HMG Co-A Reductase Inhibitors (Statins)

Over the past couple of decades, statins have been investigated as chemopreventive agents due to the demonstration that HMG-CoA reductase is overexpressed in colorectal cancer cells [133] and that statins induce apoptosis and inhibit cell growth [134, 135]. Initial enthusiasm from observational studies suggesting associations with statins on decreased overall CRC risk [136] and advanced stage CRC risk [137] was diminished by inconsistent results from recent prospective studies [138–140]. Ultimately, a phase III clinical trial of rosuvastatin was launched through the NCTN in an attempt to prove clinical benefit in early-stage colon cancer survivors (NSABP P-5, NCT01011478). However, the trial was closed in Fall 2014 due to poor accrual, in part because of the large number of patients in the US already taking a statin for cholesterol-lowering purposes. As such, there are currently no recommendations for statin use in the setting of primary, secondary, or tertiary CRC prevention.

Metformin

While agreement in the literature is not uniform [141], a growing evidence of population-based studies shows lower levels of cancer incidence (including CRC) and cancer-specific deaths among diabetics on metformin than diabetics on other treatments [142–144]. Two non-mutually exclusive mechanisms have been proposed: (1) reduction of host insulin levels by metformin and (2) the direct action of metformin as an AMPK activator and mTOR inhibitor in neoplastic cells. A key action of metformin is activation of the LKB1/AMPK pathway (Fig. 29.4) [145]. One pivotal study demonstrated that the in vivo action of metformin is severely attenuated in liver-specific LKB1 knockout mice [146]. There is evidence that hyperinsulinemia stimulates aggressive cancer behavior. Metformin has important insulin-lowering and glucose-lowering activity in hyperinsulinemic patients with the metabolic syndrome, obesity, and/or type II diabetes [147]. Metformin has a direct growth inhibitory action [148, 149], requiring AMPK activation that leads to inhibition of mTOR activation and protein synthesis [148, 149], and reduced proliferation. Multiple investigations suggest specific relevance of these hypotheses to CRC [150–158]. In CRC mouse models, 10 weeks of treatment with metformin favorably altered mTOR pathway intermediates in colorectal polyps and resulted in decreased intestinal polyp formation [153]. In a small clinical trial of patients with colorectal aberrant crypt foci (ACF), which have been associated with CRC development, metformin 250 mg/d for 30 days reduced the number of colorectal ACF and dysplastic ACF when compared to placebo [159]. A National Cancer Institute (NCI), Division of Cancer Prevention-funded Phase IIA clinical trial of metformin 1,000 mg po bid (after 3-week upward dose titration) for a total of 3 months was conducted among obese patients with colorectal adenomas, with a primary endpoint of pS6 (by IHC) reduction in the colorectal mucosa (pre- vs. post-rectal mucosa biopsy analysis). Reports of this trial reveal no differences in the proposed rectal mucosa biomarker endpoints downstream of mTOR (NCT0131246) [160]. Currently, we await the final result of this study among other metformin-based CRC prevention trials.

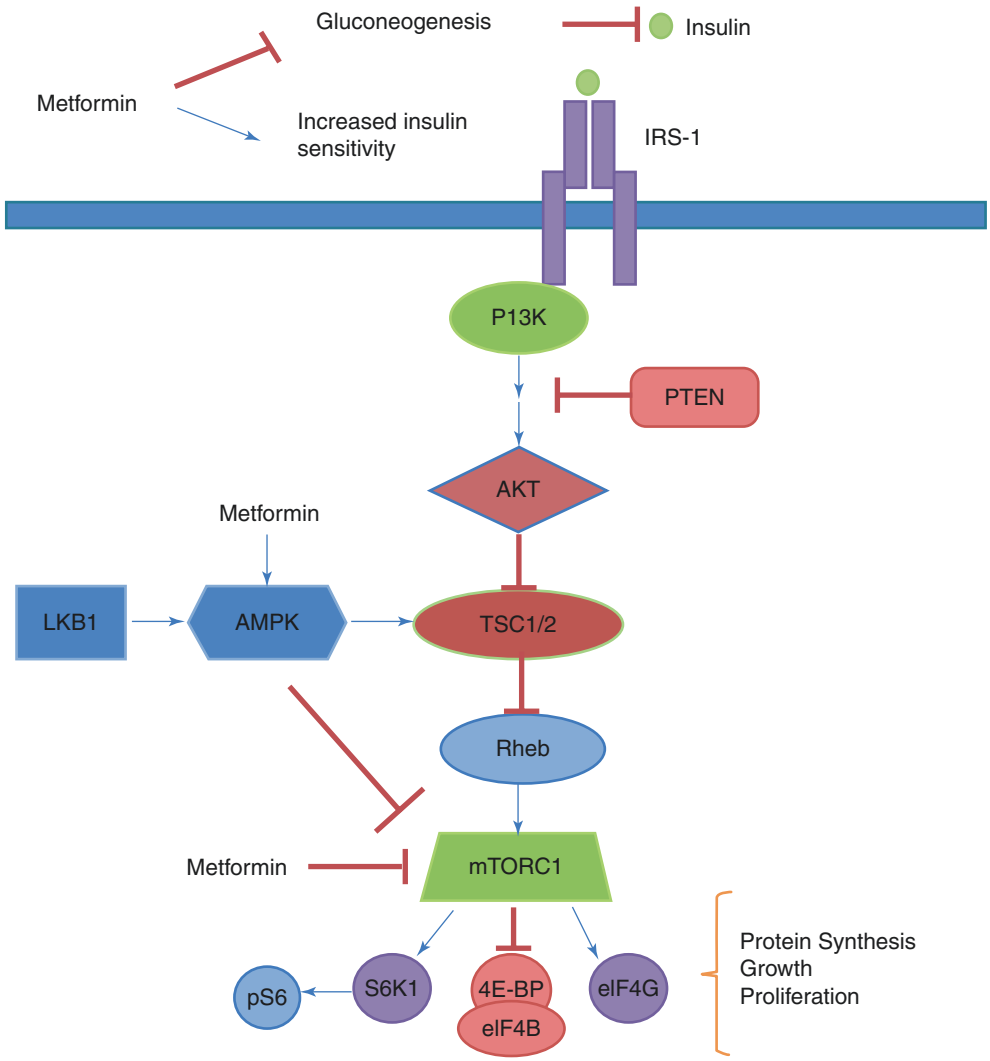


Fig. 29.4 Mechanism of action of metformin in cancer prevention. Metformin decreases insulin production indirectly by inhibiting gluconeogenesis and increasing insulin sensitivity. Lower insulin levels decrease activation of the PI3K/AKT/mTOR pathway, which is involved in many types of malignancies. Additionally, metformin also stimulates a key cellular energy regulator, 5' AMP-activated protein kinase (AMPK). Activation of AMPK inhibits formation of the mTOR complex. Metformin also directly inhibits the mTOR complex.

Polyamine Inhibitors

Polyamines are naturally occurring amino acid-derived cations found in biologic systems [161] and they are involved in numerous physiological processes, including wound repair and spermatogenesis. However, in excess, polyamines are associated with carcinogenesis in epithelial tissues, particularly within the colorectum [162, 163]. The major polyamines include putrescine, spermidine, and spermine. Polyamines themselves are derived from diet, and through conversion directly by intestinal bacteria from ornithine (a product of the urea cycle) to the polyamines, or through conversion of the rate-limiting step in polyamine synthesis, ornithine decarboxylase (ODC) [162]. Dietary arginine, which is itself a precursor to ornithine and thus the polyamines, is believed to be involved in polyamine-associated carcinogenesis. In ApcMin/+ mice, intestinal tumorigenesis results from dietary arginine supplementation, in a polyamine-dependent process that can be inhibited by NSAIDs (through induction of spermidine spermine acetyltransferase and subsequent cellular polyamine export), and the ODC inhibitor eflornithine (difluromethylornithine, DFMO) (Fig. 29.3) [8, 164]. In these studies, combination of eflornithine and NSAIDs dramatically decrease murine intestinal polyamine levels and tumorigenesis. As such, polyamine inhibitors have been investigated in a series of clinical trials in humans as CRC chemoprevention. Early phase clinical trials revealed that low doses of eflornithine could inhibit polyamines in the rectal mucosa, and the treatment was well tolerated [165, 166]. Subsequently, a phase III randomized controlled clinical trial investigated combination eflornithine 500 mg/day plus sulindac 150 mg/d versus placebos in colorectal adenoma patients over a 3-year duration [167]. Compared with both placebos, combination eflornithine and sulindac resulted in a 70% decreased adenoma recurrence rate. Impressively, the effects against high-risk adenomas (high-grade dysplasia, villous adenomas) and multiple adenomas

were >90%, and the combination regimen was very well tolerated. No clinical differences in side effects were observed when compared to placebos [167, 168]. However, in subsequent analyses, a small, non-significant and transient 8% difference in audiogram thresholds was observed without evidence of clinical hearing loss [169]. Secondary analyses from this landmark adenoma trial revealed a number of important insights on polyamine inhibition of colorectal carcinogenesis. As sulindac has both polyamine inhibitory and prostaglandin synthesis inhibitory properties, translational analyses were conducted on tissue polyamine and prostaglandins levels in the parent study. Importantly, rectal tissue biomarker alterations affecting polyamines (but not prostaglandins) were observed after eflornithine/sulindac treatment in the parent trial [170]. A polymorphism at ODC1 +316 is known to modify the effects of regular aspirin use on recurrent colorectal adenomas [171]. In the parent trial of adenoma risk reduction by polyamine inhibitors, investigators observed that the +316 ODC1 polymorphism modulates eflornithine/sulindac effects on adenoma recurrence [172]. In the parent trial, polyamine inhibitors were effective regardless of baseline obesity status [173]. Diet may have relevance to polyamine inhibition in CRC prevention. Certain foods are high in polyamine content, including meats, processed meats, peanut butter, nuts, beer, corn, grapefruit juice, and orange juice [174]. In APC $^{Min/+}$ mice dietary polyamine supplementation increases intestinal tissue polyamine levels [175] and decreases anticarcinogenic effects of sulindac [176]. Consistent with these experimental results, a high dietary polyamine intake abrogated the adenoma risk-reductive effects ascribed to eflornithine/sulindac among colorectal adenoma patients in the parent trial [177]. Currently, a randomized controlled phase III clinical trial of CRC survivors is underway within the NCTN to investigate eflornithine, sulindac, or placebos on the development of high-risk adenoma or second primary CRC (NCT01349881; S0820/PACES: Preventing Adenomas of Colon with Eflornithine and Sulindac) [178]. Additionally, these polyamine inhibitors are being evaluated in a randomized trial of FAP patients (NCT01483144). While these polyamine inhibitory agents hold promise in CRC prevention, future indications must await completion of the ongoing randomized clinical trials.

Colorectal Cancer Immuno-prevention

Colorectal cancer is subjected to strong immune surveillance as evidence by the presence of tumor-specific antibodies and T cells that are found even in colonic adenomas [179, 180]. The goal of cancer vaccination is to optimize the pre-existing immune surveillance and subsequent elimination of the premalignant lesions. Recent clinical trials have shown modest improvement in DFS and OS in patients with several malignancies including melanoma [181], prostate cancer [182], and follicular lymphoma [183]. MUC1 is a glycoprotein that expresses abnormally in premalignant and malignant CRC cells, making it an ideal target for tumor vaccination [184–186]. In various animal models, MUC1 vaccine administration results in immune protection against MUC1+ tumors [187–189]. Recently, a clinical study demonstrated that administration of human tumor-associated antigen (TAA) MUC1 vaccine to 39 patients with colonic adenoma elicited high levels of anti-MUC1 IgG and produces long-lasting immune memory. The vaccine was safe with minimal side effects. Lack of response in 22/39 individuals was correlated with high levels of circulating myeloid-derived suppressor cells (MDSCs), but not regulatory T cells at baseline [190]. Increased MDSCs, like regulatory T cells, have been demonstrated to suppress adaptive immune system [191, 192] and have been associated with advanced cancer [193]. Although the preliminary immunogenicity data appear promising at least in individuals with low baseline MDSCs, we will need further clinical data to determine whether this vaccine can translate into clinical benefit, such as reducing adenoma recurrence. It is anticipated that cancer vaccination will assume a greater role in CRC prevention in the future.

Anal Cancer

Although still rare, the incidence of anal cancer has risen substantially with a 3-fold increase in men and 1.7-fold in women [194]. Important risk factors include men who have sex with other men (MSM), HPV infection, human immunodeficiency virus (HIV) infection, chronic immunosuppression other than HIV infection, and smoking. There is a markedly higher incidence of anal intraepithelial neoplasia (AIN) and anal cancer in HIV-infected men, particularly MSM. In a report of data from 13 cohorts including 34,189 HIV-infected and 114,260 HIV-uninfected individuals, the unadjusted anal cancer incidence rates per 100,000 person-years were 131 for HIV-infected MSM, 46 for other HIV-infected men, and 2 for HIV-uninfected men [195]. As a result, some public health institutions recommend anal cancer screening for high-risk populations [195]. Currently, there are no randomized trials demonstrating improved survival with anal dysplasia screening. Other caveats include absence of uniform and effective treatment for AIN and unknown progression rate from AIN to anal cancer [196]. Emerging evidence suggests that use of the HPV vaccine reduces the rates of anal intraepithelial neoplasia, including grade 2 or 3, among MSM men. In a phase III HPV vaccination trial that included 598 MSM men, the per protocol efficacy for prevention of HPV related all-grade AIN was 77.5% and against AIN2/3 was 74.9% [197]. No adverse event from HPV vaccine was observed. The positive results from this study, among others, prompted the Advisory Committee on

Immunization Practices (ACIP) to recommend HPV vaccination in males in 2011 in addition to the prior recommendation for females in 2006. The long-term impact of HPV vaccine on anal cancer risk and mortality remains to be seen.

Esophageal Cancer

Esophageal cancer is the eighth most common cancer and the sixth most common cause of cancer death [198]. Since the 1970s, the incidence of esophageal adenocarcinoma has risen dramatically from 10% of all esophageal cancer cases in the United States to more than 60% [199] with a concomitant decline in squamous cell carcinoma [200]. Obesity, smoking, alcohol, and gastroesophageal reflux are linked to Barrett's esophagus (BE) and subsequent esophageal adenocarcinoma. Barrett's esophagus is a premalignant condition that carries an annual risk of developing cancer from 0.1% to 0.4% per year [201–203]. Consequently, the American College of Gastroenterology (ACG) recommends endoscopic surveillance every 3–5 years for BE patients without dysplasia [204, 205]. For patients with high-grade dysplasia or intramucosal carcinoma, ACG recommends endoscopic eradication [204]. Guidelines recommend either surveillance or endoscopic eradication for patients with low-grade dysplasia, but most experts favor endoscopic ablation to prevent dysplasia progression.

Endoscopic ablative therapies employ radiofrequency, thermal, or photochemical energy to eradicate the abnormal Barrett's mucosa. Radiofrequency ablation (RFA) is the most commonly used technique, which delivers radiofrequency energy to the esophageal mucosa by an inflatable balloon that contains a coil electrode array [206]. RFA is highly effective with complete eradication of dysplastic Barrett's mucosa by more than 90% [207, 208]. RFA was shown to reduce progression from Barrett's esophagitis to dysplasia (3.6% vs. 16.3%) and neoplasia (1.2% vs. 9.3%) relative to sham therapy [209]. However, there is a substantial risk of recurrence following RFA, highlighting the need for ongoing endoscopic surveillance [210]. Endoscopic spray cryotherapy is a newer ablative technique that freezes the Barrett's mucosa with low-pressure liquid nitrogen or carbon dioxide gas. Observational data suggest that cryotherapy is highly effective, with an eradication rate of 94% for high-grade dysplasia, 89% for dysplasia, 77% for intramucosal cancer, and 55% for metaplasia [211]. The procedure is safe with no major complications. Long-term data are lacking and RFA is still the most commonly used technique. Photodynamic therapy is another ablative technique that utilizes photochemical to produce cytotoxicity after exposure to light and O_2. It is rarely used due to potential serious complications, such as esophageal stricture and high rate of progression to malignancy.

Endoscopic mucosal resection (EMR) involves removal of esophageal mucosa down to the submucosa and provides large tissue specimens for histological examination and pathological staging. Endoscopic resection is effective with complete eradication rate of 94% for high-grade dysplasia and 89% for all Barrett's mucosa [208]. For large lesions, EMR should be combined with RFA to reduce the risk of EMR-associated complications such as stricture. For instance, a study found that the esophageal stenosis was significantly higher in patients who underwent stepwise radical EMR compared to those who had EMR followed by RFA (88% vs. 14%) [212].

Proton pump inhibitor (PPI) therapy is recommended for all BE patients given the clinical benefits of reflux control and potential as chemoprevention. PPIs reduce esophageal mucosal irritation by suppressing reflux acid, which is known to cause DNA damage in Barrett's epithelial cells [213]. A retrospective study found that the use of PPI after BE diagnosis was independently associated with 75% reduced risk of dysplasia [214]. Similarly, a meta-analysis from 7 observational studies ($n = 2{,}813$) also found that PPI use was associated with a 71% reduction in risk of high-grade dysplasia and carcinoma [215]. The long-term consequence of acid suppression on this disease is unknown as prospective data are lacking. Moreover, it is a fact that the incidence of EAC continues to rise throughout the PPI era. The doses of PPI or H2 blockers required to treat reflux symptoms are significantly lower than the dose required for full acid suppression. A prospective study that focused on the progression to dysplasia in a cohort of 68 BE patients showed that profound acid suppression (omeprazole 40 mg BID) may cause partial regression of intestinal metaplasia compared to mild acid suppression (ranitidine 150 mg BID) [216]. Larger interventional trials are needed to evaluate the role of higher PPI dose and/or a combination of PPI and other agents in esophageal cancer prevention.

Nonsteroidal anti-inflammatory drugs and aspirin appear to have a chemopreventive effect against BE and EC. Preclinical studies showed that Barrett's metaplastic and dysplastic cells overexpressed COX-2 [217], and suppression of COX-2 by celecoxib in rat model systems resulted in decreased esophagitis and prevention of metaplasia and EC [218]. Multiple observational studies estimated an approximately 40% EC risk reduction associated with intake of aspirin or NSAIDs [219–221]. The combination of statins and NSAIDs appear to have an additive effect (HR 0.22) [222]. However, the phase IIb multicenter, randomized, placebo-controlled Chemoprevention for Barrett's Esophagus Trial (CBET) revealed no difference in the rate of cancer progression in BE patients taking 200 mg celecoxib BID compared to placebo after 48-week follow-up [223]. Due to the potential adverse effects such as GI bleeding and cardiovascular toxicities, NSAIDs cannot be recommended for EC chemo-

prevention at this time. On the other hand, aspirin is a safer alternative when given with PPI, but more prospective data are needed. A large multicenter phase III trial evaluating the efficacy and safety of esomeprazole (high versus low dose) with or without aspirin for the prevention of EC in Barrett's esophagus individuals with 10-year follow-up is currently being conducted in the United Kingdom [224].

Gastric Cancer

Gastric cancer (GC) demonstrates significant regional variation, with high incidence observed in Eastern Asia, South America, Eastern Europe, and the Middle East. The overall incidence of GC is low in the US but higher in ethnic minorities such as Asians, Hispanics, and African-Americans [225]. Since intervention in early GC (T1 lesion) results in more than 90% 5-year survival [226, 227], countries with high prevalence of GC, such as South Korea and Japan, adopted universal screening programs. In Japan, the proportion of early GC rose from 15% to as high as 57% with the introduction of screening programs [228]. Currently, there is no recommendation for universal GC screening in the US due to the lack of cost effectiveness [229]. However, screening should be considered in high-risk individuals having atrophic gastritis, intestinal metaplasia, gastric adenoma, and familial genetic syndromes including hereditary diffuse gastric cancer, familial adenomatous polyposis, Lynch, Peutz-Jeghers, and juvenile polyposis [230–232].

Gastric intestinal metaplasia (GIM) is a premalignant condition in the gastric carcinogenesis sequence through a series of well-defined precursors. These precursor lesions include nonatrophic gastritis, multifocal atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer [233]. The risk of progression to cancer is influenced by the virulence factors of the infecting *H. pylori* strain, environmental stimuli, host genetics, and extent of intestinal metaplasia [234]. The risk of malignancy can be as high as 11% in atrophic gastritis and intestinal metaplasia [235]. Limited evidence suggests that surveillance may lead to early detection of GC and improved survival in patients with precursor lesions [235, 236]. The European Society of Gastrointestinal Endoscopy recommends surveillance for GC in individuals with premalignant conditions by upper endoscopy and gastric biopsy mapping every 2–3 years [237]. In contrast, the American Society for Gastrointestinal Endoscopy suggests that the risk of progression to cancer is low for most Americans and recommends against surveillance unless other risk factors for GC are present, such as a family history of gastric cancer and Asian heritage [238].

Current guidelines recommend to screen and treat *H. pylori* in individuals with premalignant lesions given its important role in carcinogenesis of GC [237]. *H. pylori* eradication resolves non-atrophic gastritis [239, 240] and may partially regress multifocal atrophic gastritis [241]. Due to the high rates of *H. pylori* infection and GC in Latin America, a US National Clinical Trials Network (NCTN) study was conducted in the region [242]. Investigators found that *H. pylori* eradication is possible in resource-poor countries, with durable effects seen 1-year after antibiotic treatment [243]. In patients with intestinal metaplasia, *H. pylori* eradication does not appear to reverse intestinal metaplasia but may slow progression to neoplasia [244, 245]. In a randomized chemoprevention trial of gastric dysplasia, individuals with precursor lesions were treated with triple therapy with ascorbic acid, carotene, or placebo [246]. All interventions resulted in statistically significant increase in the rates of regression for atrophic gastritis (RR 4.8) and intestinal metaplasia (RR 3.1). The addition of ascorbic acid or carotene did not provide additional benefits over triple therapy. It is unclear if improvement in the precursor lesions can prevent GC. A large-scale randomized trial in China failed to demonstrate that *H. pylori* eradication led to a significant decrease in the rate of GC in all *H. pylori* carriers at 7.5 years [247]. Subgroup analysis revealed that *H. pylori* eradication significantly decreased the development of GC in carriers with no precursor lesions. Subsequent meta-analysis of 6 studies comprising 6,695 individuals found that *H. pylori* eradication decreased the risk of GC by 35% [248]. Overall, the chemopreventive benefit of *H. pylori* eradication appears highest in individuals with non-atrophic gastritis and atrophic gastritis, before the development of intestinal metaplasia.

There is some evidence to suggest that long-term intake of NSAIDs is associated with decreased incidence of GC according to 2 meta-analyses of observational studies [249, 250]. COX-2 plays an important role in gastric carcinogenesis as COX-2 is upregulated in *H. pylori*-induced inflammation, precursor lesions, and gastric tumors [251]. A prospective cohort study of 150 chronic celecoxib users and 216 non-users found a higher regression rate of intestinal metaplasia in users than non-users (42% vs. 20%) after *H. pylori* eradication [252]. A small, randomized, placebo-controlled trial evaluating the effect of celecoxib on 60 patients following *H. pylori* eradication also found increased regression of precursor lesions in the celecoxib arm after 3 months [253]. In contrast, a larger, double-blind, randomized, placebo-controlled trial involving 213 subjects did not find any difference in intestinal metaplasia regression in those who took rofecoxib versus placebo for 2 years [254]. Currently, NSAIDs are not recommended for GC chemoprevention due to an unfavorable risk and benefit ratio.

In general, the chemopreventive benefit of vitamin supplementation is weak based on results from several trials conducted in countries with high GC prevalence. As mentioned earlier, the addition of ascorbic acid or carotene did not provide

additional benefits over triple therapy in causing regression of premalignant lesions [246]. Two other randomized trials, one conducted in China [255] and another in Venezuela [256], failed to find any difference in progression/regression of gastric precancerous lesions between vitamin supplements (ascorbic acid, vitamin E, beta-carotene, and selenium) and placebo.

Pancreas Cancer

Pancreas adenocarcinoma is one of the most aggressive solid tumors faced in clinical practice. Unfortunately, no effective screening measures have been established for this disease, and little has been achieved in the realm of therapeutic prevention. Retrospective analysis of data in the Alpha-Tocopherol Beta Carotene Cancer Prevention (ATBC) study involving >29,000 male smokers ages 50–69 demonstrated no benefit of either alpha-tocopherol or beta carotene on incidence or mortality of pancreas cancer [257]. Prospective clinical trials of pancreas cancer prevention are few and far between. Cancer prevention researchers have aimed at precancerous conditions in order to test new preventive strategies. In particular, patients with intraductal papillary mucinous neoplasms (IPMNs) have been investigated as a population at high-risk for developing pancreas cancer. In a small clinical trial, sulindac treatment resulted in decreased branch duct diameter and mural height in 10 IPMN patients when compared to 12 IPMN patients in the control (no sulindac) group [258]. Molecularly targeted therapeutics have been investigated as pancreas cancer prevention in IPMN patients. Erlotinib (an epidermal growth factor receptor [EGFR] tyrosine kinase inhibitor) is approved by the US Food and Drug Administration (FDA) for treatment of advanced pancreas adenocarcinoma in combination with gemcitabine. Preclinical studies have demonstrated that the EGFR pathway is important in the progression of IPMN lesions [259, 260]. In order to test the effect of erlotinib in a population of IPMN patients prior to pancreaticoduodenectomy, a Phase IIa study of erlotinib in IPMN patients was launched through the US NCI-Division of Cancer Prevention Chemoprevention Consortium [261]. Erlotinib 100 mg by mouth daily was given for 21–42 days prior to resection. Unfortunately, the trial was closed due to low accrual, with only 6 patients on-study. Erlotinib levels were detected both in plasma and in resected tissue among study participants, and interestingly the one patient having the highest serum and tissue erlotinib levels had a clinical response in the short time on-treatment. This study reveals some of the challenges of studying a therapeutic preventive agent in the setting of pancreas cancer prevention, including the relative rarity of the pre-cancerous condition (IPMN), as well as the heterogeneity of treatment approaches for IPMN patients, and resultant challenges to accrual.

Hepatobiliary Cancers

Liver cancer is a deadly disease, which unfortunately has been on the rise in the United States in recent years [2]. Therapeutic prevention of liver cancer has been limited; however, a few notable advances have been made in the field. Due to their anti-inflammatory effects, aspirin and other NSAIDs have been investigated in relation to hepatocellular carcinoma (HCC) prevention. In a retrospective study of the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort, aspirin use vs. no aspirin use was associated with a significant 41% decreased risk of HCC, which was independent of other key clinical factors [262]. Of note, non-aspirin NSAID use was not associated with a decreased risk of HCC in this same observational report [262].

S-adenosylmethionine (SAMe) has been investigated as HCC prevention. SAMe is a substrate for numerous biochemical pathways, and has an outstanding safety profile [263, 264]. Animal studies have revealed that SAMe deficiency increases HCC risk [265–267], and SAMe supplementation reduces HCC risk [268, 269]. Given these properties, SAMe was investigated in a small, randomized, double-blind, placebo-controlled clinical trial of HCV patients with advanced cirrhosis as a high-risk group [270]. After a 24-week intervention, blood levels of SAMe were demonstrably increased in the intervention group. However, no effect on serum alphafetoprotein (AFP) was detected, nor were there effects on markers of liver function, hepatitis C virus levels, oxidative stress, or quality of life. As such, follow-up studies are not planned.

Although beyond the scope of this chapter, prevention of hepatitis B virus (HBV) through vaccination does represent a means of primary HCC prevention. Along these lines, curing hepatitis C virus (HCV) infection decreases the risk of HCC. This has been demonstrated in the era of interferon treatments where sustained HCV response was shown to result in lower risk of HCC [271]. Newer agents such as the direct-acting anti-viral treatments (sofosbuvir and ledipasvir) along with HCV protease inhibitors have outstanding efficacy against HCV. Although the cost of these new HCV treatments is a major consideration, these agents have generated excitement about the possibility of curing HCV. While the long-term effects on HCC prevention after treatment with the new HCV medications are unknown, it is expected that such agents will dramatically reduce the risk of HCC in the population under treatment.

Conclusion

Prevention of GI malignancies remains an important goal, due to the tremendous global health burden of GI cancers. While much is to be learned, real progress has been made – particularly in our understanding of the roles of diet, lifestyle

factors, and chemopreventive agents in the prevention of CRC among other GI cancers. Clearly, there is a need for more high-quality experimental, epidemiologic, and particularly clinical trials-based evidence in support of effective cancer preventive interventions.

Acknowledgments Funding: Support for this work comes from a University of California Irvine Department of Medicine Research Grant.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. Globocan 2012 v1. 0, cancer incidence and mortality worldwide: Iarc cancerbase no. 11. 2013. Available from: globocan iarc fr. 2014.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34. https://doi.org/10.3322/caac.21551. Epub 2019 Jan 8. PMID: 30620402.
3. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759–67.
4. Cancer Statistics. Retrieved February 8, from http://www.cancer.gov/about-cancer/what-is-cancer/statistics. 2016. National Cancer Institute.
5. Chan D, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One. 2011;6(6):e20456.
6. Chan AT, Tranah GJ, Giovannucci EL, Hunter DJ, Fuchs CS. Genetic variants in the ugt1a6 enzyme, aspirin use, and the risk of colorectal adenoma. J Natl Cancer Inst. 2005;97(6):457–60.
7. Girard H, Butler LM, Villeneuve L, Millikan RC, Sinha R, Sandler RS, et al. Ugt1a1 and ugt1a9 functional variants, meat intake, and colon cancer, among caucasians and african-americans. Mutat Res. 2008;644(1):56–63.
8. Zell JA, Ignatenko NA, Yerushalmi HF, Ziogas A, Besselsen DG, Gerner EW, et al. Risk and risk reduction involving arginine intake and meat consumption in colorectal tumorigenesis and survival. Int J Cancer. 2007;120(3):459–68.
9. Yerushalmi HF, Besselsen DG, Ignatenko NA, Blohm-Mangone KA, Padilla-Torres JL, Stringer DE, et al. The role of no synthases in arginine-dependent small intestinal and colonic carcinogenesis. Mol Carcinog. 2006;45(2):93–105.
10. Key TJ, Schatzkin A, Willett WC, Allen NE, Spencer EA, Travis RC. Diet, nutrition and the prevention of cancer. Public Health Nutr. 2004;7(1a):187–200.
11. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi F, Benbrahim-Tallaa L, et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 2015;16(16):1599.
12. McCullough ML, Giovannucci EL. Diet and cancer prevention. Oncogene. 2004;23(38):6349–64.
13. Moore MA, Park CB, Tsuda H. Soluble and insoluble fiber influences on cancer development. Crit Rev Oncol Hematol. 1998;27(3):229–42.
14. Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van Den Brandt PA, Buring JE, et al. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. J Natl Cancer Inst. 2007;99(19):1471–83.
15. Lee JE, Chan AT. Fruit, vegetables, and folate: cultivating the evidence for cancer prevention. Gastroenterology. 2011;141(1):16.
16. Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. N Engl J Med. 2000;342(16):1149–55.
17. Lanza E, Yu B, Murphy G, Albert PS, Caan B, Marshall JR, et al. The polyp prevention trial–continued follow-up study: no effect of a low-fat, high-fiber, high-fruit, and-vegetable diet on adenoma recurrence eight years after randomization. Cancer Epidemiol Biomark Prev. 2007;16(9):1745–52.
18. Jacobs ET, Giuliano AR, Roe DJ, Guillén-Rodríguez JM, Hess LM, Alberts DS, et al. Intake of supplemental and total fiber and risk of colorectal adenoma recurrence in the wheat bran fiber trial. Cancer Epidemiol Biomark Prev. 2002;11(9):906–14.
19. Lanza E, Hartman TJ, Albert PS, Shields R, Slattery M, Caan B, et al. High dry bean intake and reduced risk of advanced colorectal adenoma recurrence among participants in the polyp prevention trial. J Nutr. 2006;136(7):1896–903.
20. Bobe G, Sansbury LB, Albert PS, Cross AJ, Kahle L, Ashby J, et al. Dietary flavonoids and colorectal adenoma recurrence in the polyp prevention trial. Cancer Epidemiol Biomark Prev. 2008;17(6):1344–53.
21. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Hu FB, Mayer RJ, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage iii colon cancer. JAMA. 2007;298(7):754–64.
22. Van Blarigan EL, Meyerhardt JA. Role of physical activity and diet after colorectal cancer diagnosis. J Clin Oncol. 2059;2014:7799.
23. McCullough ML, Gapstur SM, Shah R, Jacobs EJ, Campbell PT. Association between red and processed meat intake and mortality among colorectal cancer survivors. J Clin Oncol. 2049;2013:1126.
24. Zhu Y, Wu H, Wang PP, Savas S, Woodrow J, Wish T, et al. Dietary patterns and colorectal cancer recurrence and survival: a cohort study. BMJ Open. 2013;3(2):e002270.
25. Zell JA, Honda J, Ziogas A, Anton-Culver H. Survival after colorectal cancer diagnosis is associated with colorectal cancer family history. Cancer Epidemiol Biomark Prev. 2008;17(11):3134–40.
26. Zell JA, Ziogas A, Bernstein L, Clarke CA, Deapen D, Largent JA, et al. Meat consumption, nonsteroidal anti-inflammatory drug use, and mortality among colorectal cancer patients in the California teachers study. Cancer Prev Res. 2010;3(7):865–75.
27. Meyerhardt JA, Sato K, Niedzwiecki D, Ye C, Saltz LB, Mayer RJ, et al. Dietary glycemic load and cancer recurrence and survival in patients with stage iii colon cancer: findings from calgb 89803. J Natl Cancer Inst. 2012;104(22):1702–11.
28. Fuchs MA, Sato K, Niedzwiecki D, Ye X, Saltz LB, Mayer RJ, et al. Sugar-sweetened beverage intake and cancer recurrence and survival in calgb 89803 (alliance). PLoS One. 2014;9(6):e99816.
29. Guercio BJ, Sato K, Niedzwiecki D, Ye X, Saltz LB, Mayer RJ, et al. Coffee intake, recurrence, and mortality in stage iii colon cancer: results from calgb 89803 (alliance). J Clin Oncol. 2061;2015:5062.
30. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands cohort study. Int J Cancer. 2011;129(11):2681–93.
31. Ren J-S, Kamangar F, Forman D, Islami F. Pickled food and risk of gastric cancer - a systematic review and meta-analysis of english and chinese literature. Cancer Epidemiol Biomark Prev. 2012;21:905.
32. Shimazu T, Wakai K, Tamakoshi A, Tsuji I, Tanaka K, Matsuo K, et al. Association of vegetable and fruit intake with gastric cancer risk among japanese: a pooled analysis of four cohort studies. Ann Oncol. 2014;25(6):1228–33.
33. Botterweck AA, van den Brandt PA, Goldbohm RA. A prospective cohort study on vegetable and fruit consumption and stomach cancer risk in the Netherlands. Am J Epidemiol. 1998;148(9):842–53.
34. McCullough ML, Robertson AS, Jacobs EJ, Chao A, Calle EE, Thun MJ. A prospective study of diet and stomach cancer mortality in United States men and women. Cancer Epidemiol Biomark Prev. 2001;10(11):1201–5.

35. Tsubono Y, Nishino Y, Komatsu S, Hsieh C-C, Kanemura S, Tsuji I, et al. Green tea and the risk of gastric cancer in Japan. N Engl J Med. 2001;344(9):632–6.
36. Chu FS, Li GY. Simultaneous occurrence of fumonisin b1 and other mycotoxins in moldy corn collected from the people's Republic of China in regions with high incidences of esophageal cancer. Appl Environ Microbiol. 1994;60(3):847–52.
37. Islami F, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F. High-temperature beverages and foods and esophageal cancer risk—a systematic review. Int J Cancer. 2009;125(3):491–524.
38. Liu J, Wang J, Leng Y, Lv C. Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: a meta-analysis of observational studies. Int J Cancer. 2013;133(2):473–85.
39. Saracco G. Primary liver cancer is of multifactorial origin: importance of hepatitis b virus infection and dietary aflatoxin. J Gastroenterol Hepatol. 1995;10(5):604–8.
40. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. Gastroenterology. 2007;132(5):1740–5.
41. Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1413–1421. e1411.
42. Sang L-X, Chang B, Li X-H, Jiang M. Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis. BMC Gastroenterol. 2013;13(1):1.
43. Kennedy O, Roderick P, Buchanan R, Fallowfield J, Hayes P, Parkes J. Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis. Aliment Pharmacol Ther. 2016;43(5):562–74.
44. WCRF/AICR CUPRF, Nutrition, physical activity and the prevention of pancreatic cancer. 2012. Available from: http://wcrf.org/sites/default/files/Pancreatic-Cancer-2012-Report.pdf.
45. Macera C, Jones D, Yore M, Ham S, Kohl H, Kimsey C Jr, et al. Prevalence of physical activity, including lifestyle activities among adults-United States, 2000-2001. Morb Mortal Wkly Rep. 2003;52(32):764–766-769.
46. Wolin K, Yan Y, Colditz G, Lee I. Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer. 2009;100(4):611–6.
47. Wolin K, Yan Y, Colditz G. Physical activity and risk of colon adenoma: a meta-analysis. Br J Cancer. 2011;104(5):882–5.
48. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104:1548. djs354.
49. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-i. Proc Nutr Soc. 2001;60(01):91–106.
50. Trojian TH, Mody K, Chain P. Exercise and colon cancer: primary and secondary prevention. Curr Sports Med Rep. 2007;6(2):120–4.
51. Kushi LH, Byers T, Doyle C, Bandera EV, McCullough M, Gansler T, et al. American cancer society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin. 2006;56(5):254–81.
52. Molmenti CLS, Hibler EA, Ashbeck EL, Thomson CA, Garcia DO, Roe D, et al. Sedentary behavior is associated with colorectal adenoma recurrence in men. Cancer Causes Control. 2014;25(10):1387–95.
53. Colbert LH, Lanza E, Ballard-Barbash R, Slattery ML, Tangrea JA, Caan B, et al. Adenomatous polyp recurrence and physical activity in the polyp prevention trial (United States). Cancer Causes Control. 2002;13(5):445–53.
54. Courneya KS, Friedenreich CM. Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. J Altern Complement Med. 1997;3(3):215–26.
55. Irwin ML, Crumley D, McTiernan A, Bernstein L, Baumgartner R, Gilliland FD, et al. Physical activity levels before and after a diagnosis of breast carcinoma. Cancer. 2003;97(7):1746–57.
56. Haydon AM, MacInnis RJ, English DR, Giles GG. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. Gut. 2006;55(1):62–7.
57. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, et al. Physical activity and survival after colorectal cancer diagnosis. J Clin Oncol. 2006;24(22):3527–34.
58. Meyerhardt JA, Giovannucci EL, Ogino S, Kirkner GJ, Chan AT, Willett W, et al. Physical activity and male colorectal cancer survival. Arch Intern Med. 2009;169(22):2102–8.
59. Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, et al. Impact of physical activity on cancer recurrence and survival in patients with stage iii colon cancer: findings from calgb 89803. J Clin Oncol. 2006;24(22):3535–41.
60. Meyerhardt JA, Ogino S, Kirkner GJ, Chan AT, Wolpin B, Ng K, et al. Interaction of molecular markers and physical activity on mortality in patients with colon cancer. Clin Cancer Res. 2009;15(18):5931–6.
61. Morikawa T, Kuchiba A, Yamauchi M, Meyerhardt JA, Shima K, Nosho K, et al. Association of ctnnb1 (β-catenin) alterations, body mass index, and physical activity with survival in patients with colorectal cancer. JAMA. 2011;305(16):1685–94.
62. Yamauchi M, Lochhead P, Imamura Y, Kuchiba A, Liao X, Qian ZR, et al. Physical activity, tumor ptgs2 expression, and survival in patients with colorectal cancer. Cancer Epidemiol Biomark Prev. 2013;22(6):1142–52.
63. Courneya KS, Booth C, Gill S, O'Brien P, Vardy J, Friedenreich C, et al. The colon health and life-long exercise change trial: a randomized trial of the national cancer institute of Canada clinical trials group. Curr Oncol. 2008;15(6):271.
64. Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath CW Jr. Diabetes mellitus and pancreatic cancer mortality in a prospective cohort of United States adults. Cancer Causes Control. 1998;9(4):403–10.
65. Wannamethee S, Shaper A, Walker M. Physical activity and risk of cancer in middle-aged men. Br J Cancer. 2001;85(9):1311.
66. Leitzmann MF, Koebnick C, Freedman ND, Park Y, Ballard-Barbash R, Hollenbeck A, et al. Physical activity and esophageal and gastric carcinoma in a large prospective study. Am J Prev Med. 2009;36(2):112–9.
67. Research. WCRFIAIfC, Continuous update project report: diet N, physical activity and liver cancer., 2015.
68. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA. 2001;286(8):921–9.
69. Inoue M, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. Am J Epidemiol. 2008;168(4):391–403.
70. Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE. Obesity, recreational physical activity, and risk of pancreatic cancer in a large us cohort. Cancer Epidemiol Biomark Prev. 2005;14(2):459–66.
71. Wolin KY, Carson K, Colditz GA. Obesity and cancer. Oncologist. 2010;15(6):556–65.
72. Campbell PT, Cotterchio M, Dicks E, Parfrey P, Gallinger S, McLaughlin JR. Excess body weight and colorectal cancer risk in Canada: associations in subgroups of clinically defined familial risk of cancer. Cancer Epidemiol Biomark Prev. 2007;16(9):1735–44.
73. Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013;8(1):e53916.

74. Rapp K, Klenk J, Ulmer H, Concin H, Diem G, Oberaigner W, et al. Weight change and cancer risk in a cohort of more than 65 000 adults in Austria. Ann Oncol. 2008;19(4):641–8.
75. Christou NV, Lieberman M, Sampalis F, Sampalis JS. Bariatric surgery reduces cancer risk in morbidly obese patients. Surg Obes Relat Dis. 2008;4(6):691–5.
76. Jacobs ET, Martínez ME, Alberts DS, Jiang R, Lance P, Lowe KA, et al. Association between body size and colorectal adenoma recurrence. Clin Gastroenterol Hepatol. 2007;5(8):982–90.
77. Kim M, Jung S, Kim C, Chung T, Yoo C, Park N. Metabolic syndrome is associated with increased risk of recurrent colorectal adenomas in korean men. Int J Obes. 2012;36(7):1007–11.
78. Scarpa M, Ruffolo C, Erroi F, Fiorot A, Basato S, Pozza A, et al. Obesity is a risk factor for multifocal disease and recurrence after colorectal cancer surgery: a case-control study. Anticancer Res. 2014;34(10):5735–41.
79. Yamaji Y, Okamoto M, Yoshida H, Kawabe T, Wada R, Mitsushima T, et al. The effect of body weight reduction on the incidence of colorectal adenoma. Am J Gastroenterol. 2008;103(8):2061–7.
80. Laiyemo AO, Doubeni C, Badurdeen DS, Murphy G, Marcus PM, Schoen RE, et al. A prospective study of obesity, weight change and the risk of adenoma recurrence. Endoscopy. 2012;44(9):813.
81. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of us adults. N Engl J Med. 2003;348(17):1625–38.
82. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Benson AB, Macdonald JS, et al. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. Cancer. 2003;98(3):484–95.
83. Parker E, Folsom A. Intentional weight loss and incidence of obesity-related cancers: the Iowa women's health study. Int J Obes. 2003;27(12):1447–52.
84. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Nelson H, et al. Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage iii colon cancer: findings from cancer and leukemia group b 89803. J Clin Oncol. 2008;26(25):4109–15.
85. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569–78.
86. Stein D, El-Serag H, Kuczynski J, Kramer J, Sampliner R. The association of body mass index with barrett's oesophagus. Aliment Pharmacol Ther. 2005;22(10):1005–10.
87. Duggan C, Onstad L, Hardikar S, Blount PL, Reid BJ, Vaughan TL. Association between markers of obesity and progression from barrett's esophagus to esophageal adenocarcinoma. Clin Gastroenterol Hepatol. 2013;11(8):934–43.
88. Latino-Martel P, Cottet V, Druesne-Pecollo N, Pierre FH, Touillaud M, Touvier M, et al. Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: a review of the evidence. Crit Rev Oncol Hematol. 2016;99:308.
89. Yang B, Yang HP, Ward KK, Sahasrabuddhe VV, McGlynn KA. Bariatric surgery and liver cancer in a consortium of academic medical centers. Obes Surg. 2016;26(3):696–700. https://doi.org/10.1007/s11695-016-2051-1.
90. Reddy BS, Maruyama H, Kelloff G. Dose-related inhibition of colon carcinogenesis by dietary piroxicam, a nonsteroidal antiinflammatory drug, during different stages of rat colon tumor development. Cancer Res. 1987;47(20):5340–6.
91. Boolbol SK, Dannenberg AJ, Chadburn A, Martucci C, Guo XJ, Ramonetti JT, et al. Cyclooxygenase-2 overexpression and tumor formation are blocked by sulindac in a murine model of familial adenomatous polyposis. Cancer Res. 1996;56(11):2556–60.
92. Barnes CJ, Lee M. Chemoprevention of spontaneous intestinal adenomas in the adenomatous polyposis coli min mouse model with aspirin. Gastroenterology. 1998;114(5):873–7.
93. Jacoby RF, Seibert K, Cole CE, Kelloff G, Lubet RA. The cyclooxygenase-2 inhibitor celecoxib is a potent preventive and therapeutic agent in the min mouse model of adenomatous polyposis. Cancer Res. 2000;60(18):5040–4.
94. Reddy BS. Studies with the azoxymethane-rat preclinical model for assessing colon tumor development and chemoprevention. Environ Mol Mutagen. 2004;44(1):26–35.
95. Hu Y, Le Leu RK, Young GP. Sulindac corrects defective apoptosis and suppresses azoxymethane-induced colonic oncogenesis in p53 knockout mice. Int J Cancer. 2005;116(6):870–5.
96. Chan AT, Giovannucci EL, Schernhammer ES, Colditz GA, Hunter DJ, Willett WC, et al. A prospective study of aspirin use and the risk for colorectal adenoma. Ann Intern Med. 2004;140(3):157–66.
97. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA. 2005;294(8):914–23.
98. Mahipal A, Anderson KE, Limburg PJ, Folsom AR. Nonsteroidal anti-inflammatory drugs and subsite-specific colorectal cancer incidence in the Iowa women's health study. Cancer Epidemiol Biomark Prev. 2006;15(10):1785–90.
99. Shaheen NJ, Straus WL, Sandler RS. Chemoprevention of gastrointestinal malignancies with nonsteroidal anti inflammatory drugs - a review. Cancer. 2002;94(4):950–63.
100. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst. 2007;99(8):608–15.
101. Labayle D, Fischer D, Vielh P, Drouhin F, Pariente A, Bories C, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology. 1991;101(3):635–9.
102. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med. 1993;328(18):1313–6.
103. Nugent KP, Farmer KCR, Spigelman AD, Williams CB, Phillips RKS. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell-proliferation in patients with familial adenomatous polyposis. Br J Surg. 1993;80(12):1618–9.
104. Steinbach G, Lynch PM, Phillips RKS, Wallace MH, Hawk E, Gordon GB, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med. 2000;342(26):1946–52.
105. Higuchi T, Iwama T, Yoshinaga K, Toyooka M, Taketo MM, Sugihara K. A randomized, double-blind, placebo-controlled trial of the effects of rofecoxib, a selective cyclooxygenase-2 inhibitor, on rectal polyps in familial adenomatous polyposis patients. Clin Cancer Res. 2003;9(13):4756–60.
106. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature. 1971;231(25):232–5.
107. Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. Cell. 1998;93(5):705–16.
108. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med. 2006;355(9):873–84.
109. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med. 2003;348(10):883–90.
110. Solomon SD, Pfeffer MA, McMurray JJ, Fowler R, Finn P, Levin B, et al. Effect of celecoxib on cardiovascular events and blood

pressure in two trials for the prevention of colorectal adenomas. Circulation. 2006;114(10):1028–35.
111. Force UPST. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: Us preventive services task force recommendation statement. Ann Intern Med. 2007;146(5):361.
112. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA. 2009;302(6):649–58.
113. Zell JA, Ziogas A, Bernstein L, Clarke CA, Deapen D, Largent JA, et al. Nonsteroidal anti-inflammatory drugs. Cancer. 2009;115(24):5662–71.
114. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of cox-2. N Engl J Med. 2007;356(21):2131–42.
115. Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, et al. Aspirin use, tumor pik3ca mutation, and colorectal-cancer survival. N Engl J Med. 2012;367(17):1596–606.
116. Domingo E, Church DN, Sieber O, Ramamoorthy R, Yanagisawa Y, Johnstone E, et al. Evaluation of pik3ca mutation as a predictor of benefit from nonsteroidal anti-inflammatory drug therapy in colorectal cancer. J Clin Oncol. 2050;2013:0322.
117. Kothari N, Kim R, Jorissen RN, Desai J, Tie J, Wong H-L, et al. Impact of regular aspirin use on overall and cancer-specific survival in patients with colorectal cancer harboring a pik3ca mutation. Acta Oncol. 2015;54(4):487–92.
118. Ishikawa H, Mutoh M, Suzuki S, Tokudome S, Saida Y, Abe T, et al. The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumours in asian patients: a randomised trial. Gut. 2014;63(11):1755. https://doi.org/10.1136/gutjnl-2013-305827.
119. Drew DA, Goh G, Mo A, Grady JJ, Forouhar F, Egan G, et al. Colorectal polyp prevention by daily aspirin use is abrogated among active smokers. Cancer Causes Control. 2016;27(1):93–103.
120. Jacobs ET, Jurutka PW, Martínez ME, Alberts DS. Vitamin d, calcium, and colorectal neoplasia: new insights on mechanisms of action. Cancer Prev Res. 2009;2(3):197–9.
121. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin d and folate: molecular mechanisms. Nat Rev Cancer. 2003;3(8):601–14.
122. Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D, et al. Diet and risk of colorectal cancer in a cohort of finnish men. Cancer Causes Control. 1999;10(5):387–96.
123. Garland C, Barrett-Connor E, Rossof A, Shekelle R, Criqui M, Paul O. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. Lancet. 1985;325(8424):307–9.
124. Wu K, Willett WC, Fuchs CS, Colditz GA, Giovannucci EL. Calcium intake and risk of colon cancer in women and men. J Natl Cancer Inst. 2002;94(6):437–46.
125. Freedman DM, Looker AC, Abnet CC, Linet MS, Graubard BI. Serum 25-hydroxyvitamin d and cancer mortality in the nhanes iii study (1988–2006). Cancer Res. 2010;70(21):8587–97.
126. Kampman E, Slattery ML, Caan B, Potter JD. Calcium, vitamin d, sunshine exposure, dairy products and colon cancer risk (United States). Cancer Causes Control. 2000;11(5):459–66.
127. Gandini S, Boniol M, Haukka J, Byrnes G, Cox B, Sneyd MJ, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin d levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer. 2011;128(6):1414–24.
128. Baron J, Beach MF, Mandel J, Van Stolk R, Haile R, Sandler R, et al. Calcium supplements for the prevention of colorectal adenomas. N Engl J Med. 1999;340(2):101–7.
129. Chu DZ, Hussey MA, Alberts DS, Meyskens FL, Fenoglio-Preiser CM, Rivkin SE, et al. Colorectal chemoprevention pilot study (swog-9041), randomized and placebo controlled: the importance of multiple luminal lesions. Clin Colorectal Cancer. 2011;10(4):310–6.
130. Baron JA, Barry EL, Mott LA, Rees JR, Sandler RS, Snover DC, et al. A trial of calcium and vitamin d for the prevention of colorectal adenomas. N Engl J Med. 2015;373(16):1519–30.
131. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006;354(7):684–96.
132. Ng K, Nimeiri HS, McCleary NJ, Abrams TA, Yurgelun MB, Cleary JM, Rubinson DA, Schrag D, Miksad R, Bullock AJ, Allen J, Zuckerman D, Chan E, Chan JA, Wolpin BM, Constantine M, Weckstein DJ, Faggen MA, Thomas CA, Kournioti C, Yuan C, Ganser C, Wilkinson B, Mackintosh C, Zheng H, Hollis BW, Meyerhardt JA, Fuchs CS. Effect of high-dose vs standard-dose vitamin D3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: the SUNSHINE randomized clinical trial. JAMA. 2019;321(14):1370–9. https://doi.org/10.1001/jama.2019.2402.
133. Hentosh P, Yuh SH, Elson CE, Peffley DM. Sterol-independent regulation of 3-hydroxy-3-methylglutaryl coenzyme a reductase in tumor cells. Mol Carcinog. 2001;32(3):154–66.
134. Cho SJ, Kim JS, Kim JM, Lee JY, Jung HC, Song IS. Simvastatin induces apoptosis in human colon cancer cells and in tumor xenografts, and attenuates colitis-associated colon cancer in mice. Int J Cancer. 2008;123(4):951–7.
135. Rao CV, Newmark HL, Reddy BS. Chemopreventive effect of farnesol and lanosterol on colon carcinogenesis. Cancer Detect Prev. 2002;26(6):419–25.
136. Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, et al. Statins and the risk of colorectal cancer. N Engl J Med. 2005;352(21):2184–92.
137. Coogan PF, Smith J, Rosenberg L. Statin use and risk of colorectal cancer. J Natl Cancer Inst. 2007;99(1):32–40.
138. Simon MS, Rosenberg CA, Rodabough RJ, Greenland P, Ockene I, Roy HK, et al. Prospective analysis of association between use of statins or other lipid-lowering agents and colorectal cancer risk. Ann Epidemiol. 2012;22(1):17–27.
139. Lee JE, Baba Y, Ng K, Giovannucci E, Fuchs CS, Ogino S, et al. Statin use and colorectal cancer risk according to molecular subtypes in two large prospective cohort studies. Cancer Prev Res. 2011;4(11):1808–15.
140. Bertagnolli MM, Hsu M, Hawk ET, Eagle CJ, Zauber AG. Statin use and colorectal adenoma risk: results from the adenoma prevention with celecoxib trial. Cancer Prev Res. 2010;3(5):588–96.
141. Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin is not associated with a decreased risk of colorectal cancer: a case-control analysis. Cancer Epidemiol Biomark Prev. 2012;21(2):280–6.
142. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ. 2005;330(7503):1304–5.
143. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care. 2006;29(2):254–8.
144. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care. 2009;32:1620.
145. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of amp-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001;108(8):1167–74.
146. Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, et al. The kinase lkb1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science. 2005;310(5754):1642–6.
147. Nestler JE, Beer NA, Jakubowicz DJ, Beer RM. Effects of a reduction in circulating insulin by metformin on serum dehydroepian-

drosterone sulfate in nondiabetic men. J Clin Endocrinol Metab. 1994;78(3):549–54.
148. Dowling RJ, Zakikhani M, Fantus IG, Pollak M, Sonenberg N. Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells. Cancer Res. 2007;67(22):10804–12.
149. Zakikhani M, Dowling R, Fantus IG, Sonenberg N, Pollak M. Metformin is an amp kinase-dependent growth inhibitor for breast cancer cells. Cancer Res. 2006;66(21):10269–73.
150. Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, et al. C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, and the risk of distal colorectal adenoma in women. Cancer Epidemiol Biomark Prev. 2006;15(4):750–5.
151. Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, et al. A prospective study of c-peptide, insulin-like growth factor-i, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomark Prev. 2005;14(4):850–5.
152. Ma J, Giovannucci E, Pollak M, Leavitt A, Tao Y, Gaziano JM, et al. A prospective study of plasma c-peptide and colorectal cancer risk in men. J Natl Cancer Inst. 2004;96(7):546–53.
153. Tomimoto A, Endo H, Sugiyama M, Fujisawa T, Hosono K, Takahashi H, et al. Metformin suppresses intestinal polyp growth in apcmin/+ mice. Cancer Sci. 2008;99(11):2136–41.
154. Zakikhani M, Dowling RJ, Sonenberg N, Pollak MN. The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of amp-activated protein kinase. Cancer Prev Res (Phila Pa). 2008;1(5):369–75.
155. Kawamoto K, Onodera H, Kondo S, Kan S, Ikeuchi D, Maetani S, et al. Expression of insulin-like growth factor-2 can predict the prognosis of human colorectal cancer patients: correlation with tumor progression, proliferative activity and survival. Oncology. 1998;55(3):242–8.
156. Oshima T, Akaike M, Yoshihara K, Shiozawa M, Yamamoto N, Sato T, et al. Clinicopathological significance of the gene expression of matrix metalloproteinase-7, insulin-like growth factor-1, insulin-like growth factor-2 and insulin-like growth factor-1 receptor in patients with colorectal cancer: insulin-like growth factor-1 receptor gene expression is a useful predictor of liver metastasis from colorectal cancer. Oncol Rep. 2008;20(2):359–64.
157. Hakam A, Yeatman TJ, Lu L, Mora L, Marcet G, Nicosia SV, et al. Expression of insulin-like growth factor-1 receptor in human colorectal cancer. Hum Pathol. 1999;30(10):1128–33.
158. Cunningham MP, Essapen S, Thomas H, Green M, Lovell DP, Topham C, et al. Coexpression of the igf-ir, egfr and her-2 is common in colorectal cancer patients. Int J Oncol. 2006;28(2):329–35.
159. Hosono K, Endo H, Takahashi H, Sugiyama M, Sakai E, Uchiyama T, et al. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. Cancer Prev Res. 2010;3(9):1077–83.
160. Zell JAMC, Morgan TR, Lawson MJ, Rezk S, Albers GC, et al. A phase IIa trial of metformin for colorectal cancer risk reduction among patients with a history of colorectal adenomas and elevated body mass index. Cancer Prev Res. 2015;8:A21.
161. Wallace HM. Polyamines in human health. Proc Nutr Soc. 1996;55(1B):419–31.
162. Gerner EW, Meyskens FL Jr. Polyamines and cancer: old molecules, new understanding. Nat Rev Cancer. 2004;4(10):781–92.
163. Jass JR, Whitehall VL, Young J, Leggett BA. Emerging concepts in colorectal neoplasia. Gastroenterology. 2002;123(3):862–76.
164. Yerushalmi HF, Besselsen DG, Ignatenko NA, Blohm-Mangone KA, Padilla-Torres JL, Stringer DE, et al. Role of polyamines in arginine-dependent colon carcinogenesis in apcmin/+ mice. Mol Carcinog. 2006;45(10):764–73.
165. Meyskens FL, Emerson SS, Pelot D, Meshkinpour H, Shassetz LR, Einspahr J, et al. Dose de-escalation chemoprevention trial of α-difluoromethylornithine in patients with colon polyps. J Natl Cancer Inst. 1994;86(15):1122–30.
166. Meyskens FL, Gerner EW, Emerson S, Pelot D, Durbin T, Doyle K, et al. Effect of α-difluoromethylornithine on rectal mucosal levels of polyamines in a randomized, double-blinded trial for colon cancer prevention. J Natl Cancer Inst. 1998;90(16):1212–8.
167. Meyskens FL, McLaren CE, Pelot D, Fujikawa S, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. Cancer Prev Res. 2008;1(1):32–8.
168. Zell JA, Pelot D, Chen W-P, McLaren CE, Gerner EW, Meyskens FL. Risk of cardiovascular events in a randomized placebo-controlled, double-blind trial of difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas. Cancer Prev Res. 2009;2(3):209–12.
169. McLaren CE, Fujikawa-Brooks S, Chen W-P, Gillen DL, Pelot D, Gerner EW, et al. Longitudinal assessment of air conduction audiograms in a phase iii clinical trial of dfmo and sulindac for prevention of sporadic colorectal adenomas. Cancer Prev Res (Phila). 2008;1(7):514.
170. Thompson PA, Wertheim BC, Zell JA, Chen W-P, McLaren CE, LaFleur BJ, et al. Levels of rectal mucosal polyamines and prostaglandin e2 predict ability of dfmo and sulindac to prevent colorectal adenoma. Gastroenterology. 2010;139(3):797–805. e791.
171. Martínez ME, O'Brien TG, Fultz KE, Babbar N, Yerushalmi H, Qu N, et al. Pronounced reduction in adenoma recurrence associated with aspirin use and a polymorphism in the ornithine decarboxylase gene. Proc Natl Acad Sci. 2003;100(13):7859–64.
172. Zell JA, McLaren CE, Chen W-P, Thompson PA, Gerner EW, Meyskens FL. Ornithine decarboxylase-1 polymorphism, chemoprevention with eflornithine and sulindac, and outcomes among colorectal adenoma patients. J Natl Cancer Inst. 2010;102(19):1513–6.
173. Zell JA, Lin BS, Madson N, McLaren CE, Gerner EW, Meyskens FL. Role of obesity in a randomized placebo-controlled trial of difluoromethylornithine (dfmo)+ sulindac for the prevention of sporadic colorectal adenomas. Cancer Causes Control. 2012;23(10):1739–44.
174. Zoumas-Morse C, Rock CL, Quintana EL, Neuhouser ML, Gerner EW, Meyskens FL Jr. Development of a polyamine database for assessing dietary intake. J Am Diet Assoc. 2007;107(6):1024–7.
175. Ignatenko NA, Besselsen DG, Roy UK, Stringer DE, Blohm-Mangone KA, Padilla-Torres JL, et al. Dietary putrescine reduces the intestinal anticarcinogenic activity of sulindac in a murine model of familial adenomatous polyposis. Nutr Cancer. 2006;56(2):172–81.
176. Thomas T, Thomas TJ. Polyamine metabolism and cancer. J Cell Mol Med. 2003;7(2):113–26.
177. Raj K, Zell J, Rock C, McLaren C, Zoumas-Morse C, Gerner E, et al. Role of dietary polyamines in a phase iii clinical trial of difluoromethylornithine (dfmo) and sulindac for prevention of sporadic colorectal adenomas. Br J Cancer. 2013; 108(3):512–8.
178. Zell J, You Y, Boughey J. Paces trial: evaluating the effectiveness of eflornithine and sulindac in preventing colon adenomas. Bull Am Coll Surg. 2015;100(8):70.
179. Silk AW, Schoen RE, Potter DM, Finn OJ. Humoral immune response to abnormal muc1 in subjects with colorectal adenoma and cancer. Mol Immunol. 2009;47(1):52–6.
180. Nagorsen D, Thiel E. Clinical and immunologic responses to active specific cancer vaccines in human colorectal cancer. Clin Cancer Res. 2006;12(10):3064–9.
181. Schwartzentruber DJ, Lawson DH, Richards JM, Conry RM, Miller DM, Treisman J, et al. Gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. N Engl J Med. 2011;364(22):2119–27.

182. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-t immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411–22.
183. Schuster SJ, Neelapu SS, Gause BL, Janik JE, Muggia FM, Gockerman JP, et al. Vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival in follicular lymphoma. J Clin Oncol. 2011;29(20):2787–94.
184. Graham RA, Burchell JM, Taylor-Papadimitriou J. The polymorphic epithelial mucin: potential as an immunogen for a cancer vaccine. Cancer Immunol Immunother. 1996;42(2):71–80.
185. Hiltbold EM, Ciborowski P, Finn OJ. Naturally processed class ii epitope from the tumor antigen muc1 primes human cd4+ t cells. Cancer Res. 1998;58(22):5066–70.
186. Ajioka Y, Watanabe H, Jass J. Muc1 and muc2 mucins in flat and polypoid colorectal adenomas. J Clin Pathol. 1997;50(5):417–21.
187. Acres B, Apostolopoulos V, Balloul J-M, Wreschner D, Xing P-X, Ali-Hadji D, et al. Muc1-specific immune responses in human muc1 transgenic mice immunized with various human muc1 vaccines. Cancer Immunol Immunother. 2000;48(10):588–94.
188. Barratt-Boyes SM, Vlad A, Finn OJ. Immunization of chimpanzees with tumor antigen muc1 mucin tandem repeat peptide elicits both helper and cytotoxict-cell responses. Clin Cancer Res. 1999;5(7):1918–24.
189. Beatty PL, Narayanan S, Gariépy J, Ranganathan S, Finn OJ. Vaccine against muc1 antigen expressed in inflammatory bowel disease and cancer lessens colonic inflammation and prevents progression to colitis-associated colon cancer. Cancer Prev Res. 2010;3(4):438–46.
190. Kimura T, McKolanis JR, Dzubinski LA, Islam K, Potter DM, Salazar AM, et al. Muc1 vaccine for individuals with advanced adenoma of the colon: a cancer immunoprevention feasibility study. Cancer Prev Res. 2013;6(1):18–26.
191. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009;9(3):162–74.
192. Greten TF, Manns MP, Korangy F. Myeloid derived suppressor cells in human diseases. Int Immunopharmacol. 2011;11(7):802–7.
193. Montero AJ, Diaz-Montero CM, Kyriakopoulos CE, Bronte V, Mandruzzato S. Myeloid-derived suppressor cells in cancer patients: a clinical perspective. J Immunother. 2012;35(2):107–15.
194. Nelson RA, Levine AM, Bernstein L, Smith DD, Lai LL. Changing patterns of anal canal carcinoma in the United States. J Clin Oncol. 2013; https://doi.org/10.1200/JCO.2012.2045.2524.
195. Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, Goedert JJ, et al. Risk of anal cancer in hiv-infected and hiv-uninfected individuals in north america. Clin Infect Dis. 2012;54(7):1026–34.
196. Chiao EY, Giordano TP, Palefsky JM, Tyring S, El Serag H. Screening hiv-infected individuals for anal cancer precursor lesions: a systematic review. Clin Infect Dis. 2006;43(2):223–33.
197. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED Jr, Aranda C, Jessen H, et al. Hpv vaccine against anal hpv infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576–85.
198. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9–29. https://doi.org/10.3322/caac.21208.
199. Blot WJ, Mc Laughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol. 1999;26:2.
200. Cook M, Chow W, Devesa S. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. Br J Cancer. 2009;101(5):855–9.
201. Sikkema M, De Jonge PJ, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2010;8(3):235–44.
202. Shakhatreh MH, Duan Z, Kramer J, Naik AD, Helm A, Hinojosa-Lindsey M, et al. The incidence of esophageal adenocarcinoma in a national veterans cohort with barrett's esophagus. Am J Gastroenterol. 2014;109(12):1862–8.
203. Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L. The incidence of esophageal cancer and high-grade dysplasia in barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol. 2008;168(3):237–49.
204. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. Acg clinical guideline: diagnosis and management of barrett's esophagus. Am J Gastroenterol. 2016;111(1):30–50.
205. Association AG. American gastroenterological association medical position statement on the management of barrett's esophagus. Gastroenterology. 2011;140(3):1084–91.
206. Sharma VK, Wang KK, Overholt BF, Lightdale CJ, Fennerty MB, Dean PJ, et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of barrett's esophagus: 1-year follow-up of 100 patients (with video). Gastrointest Endosc. 2007;65(2):185–95.
207. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for barrett's esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(10):1245–55.
208. Chadwick G, Groene O, Markar SR, Hoare J, Cromwell D, Hanna GB. Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic barrett's esophagus: a critical assessment of histologic outcomes and adverse events. Gastrointest Endosc. 2014;79(5):718–731. e713.
209. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in barrett's esophagus with dysplasia. N Engl J Med. 2009;360(22):2277–88.
210. Small AJ, Sutherland SE, Hightower JS, Guarner-Argente C, Furth EE, Kochman ML, et al. Comparative risk of recurrence of dysplasia and carcinoma after endoluminal eradication therapy of high-grade dysplasia versus intramucosal carcinoma in barrett's esophagus. Gastrointest Endosc. 2015;81(5):1158–1166. e1154.
211. Canto MI, Shin EJ, Khashab MA, Molena D, Okolo P, Montgomery E, et al. Safety and efficacy of carbon dioxide cryotherapy for treatment of neoplastic barrett's esophagus. Endoscopy. 2015;47(7):582–91.
212. van Vilsteren FG, Pouw RE, Seewald S, Herrero LA, Sondermeijer CM, Visser M, et al. Stepwise radical endoscopic resection versus radiofrequency ablation for barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. Gut. 2011; https://doi.org/10.1136/gut.2010.229310.
213. Zhang HY, Hormi-Carver K, Zhang X, Spechler SJ, Souza RF. In benign barrett's epithelial cells, acid exposure generates reactive oxygen species that cause DNA double-strand breaks. Cancer Res. 2009;69(23):9083–9.
214. El-Serag HB, Aguirre TV, Davis S, Kuebeler M, Bhattacharyya A, Sampliner RE. Proton pump inhibitors are associated with reduced incidence of dysplasia in barrett's esophagus. Am J Gastroenterol. 2004;99(10):1877–83.
215. Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with barrett's oesophagus: a systematic review and meta-analysis. Gut. 2013; https://doi.org/10.1136/gutjnl-2013-305997.
216. Peters F, Ganesh S, Kuipers E, Sluiter W, Klinkenberg-Knol E, Lamers C, et al. Endoscopic regression of barrett's oesophagus during omeprazole treatment; a randomised double blind study. Gut. 1999;45(4):489–94.
217. Morris CD, Armstrong GR, Bigley G, Green H, Attwood SE. Cyclooxygenase-2 expression in the barrett's metaplasia–dysplasia–adenocarcinoma sequence. Am J Gastroenterol. 2001;96(4):990–6.
218. Oyama K, Fujimura T, Ninomiya I, Miyashita T, Kinami S, Fushida S, et al. A cox-2 inhibitor prevents the esophageal inflammation–metaplasia–adenocarcinoma sequence in rats. Carcinogenesis. 2005;26(3):565–70.

219. Nguyen DM, Richardson P, El–Serag HB. Medications (nsaids, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with barrett's esophagus. Gastroenterology. 2010;138(7):2260–6.
220. Omer ZB, Ananthakrishnan AN, Nattinger KJ, Cole EB, Lin JJ, Kong CY, et al. Aspirin protects against barrett's esophagus in a multivariate logistic regression analysis. Clin Gastroenterol Hepatol. 2012;10(7):722–7.
221. Zhang S, Zhang X, Ding X, Yang R, Huang S, Kastelein F, et al. Cyclooxygenase inhibitors use is associated with reduced risk of esophageal adenocarcinoma in patients with barrett's esophagus: a meta-analysis. Br J Cancer. 2014;110(9):2378–88.
222. Kastelein F, Spaander MC, Biermann K, Steyerberg EW, Kuipers EJ, Bruno MJ, et al. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with barrett's esophagus. Gastroenterology. 2011;141(6):2000–8.
223. Heath EI, Canto MI, Piantadosi S, Montgomery E, Weinstein WM, Herman JG, et al. Secondary chemoprevention of barrett's esophagus with celecoxib: results of a randomized trial. J Natl Cancer Inst. 2007;99(7):545–57.
224. Das D, Chilton AP, Jankowski JA. Chemoprevention of oesophageal cancer and the aspect trial. Cancer Prev II Springer. 2009;181:161–9.
225. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
226. Okada K, Fujisaki J, Yoshida T, Ishikawa H, Suganuma T, Kasuga A, et al. Long-term outcomes of endoscopic submucosal dissection for undifferentiated-type early gastric cancer. Endoscopy. 2012;44(2):122–7.
227. Choi IJ, Lee JH, Kim Y-I, Kim CG, Cho S-J, Lee JY, et al. Long-term outcome comparison of endoscopic resection and surgery in early gastric cancer meeting the absolute indication for endoscopic resection. Gastrointest Endosc. 2015;81(2):333–341. e331.
228. Shimizu S, Tada M, Kawai K. Early gastric cancer: its surveillance and natural course. Endoscopy. 1995;27(1):27–31.
229. Dan YY, So J, Yeoh KG. Endoscopic screening for gastric cancer. Clin Gastroenterol Hepatol. 2006;4(6):709–16.
230. Evans JA, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Fisher DA, et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc. 2015;82(1):1–8.
231. Yoon H, Kim N. Diagnosis and management of high risk group for gastric cancer. Gut Liver. 2015;9(1):5.
232. Choi IJ. Endoscopic gastric cancer screening and surveillance in high-risk groups. Clini Endosc. 2014;47(6):497–503.
233. Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. Lancet. 1975;306(7924):58–60.
234. Ohata H, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, et al. Progression of chronic atrophic gastritis associated with helicobacter pylori infection increases risk of gastric cancer. Int J Cancer. 2004;109(1):138–43.
235. Whiting J, Sigurdsson A, Rowlands D, Hallissey M, Fielding J. The long term results of endoscopic surveillance of premalignant gastric lesions. Gut. 2002;50(3):378–81.
236. Rokkas T, Filipe M, Sladen G. Detection of an increased incidence of early gastric cancer in patients with intestinal metaplasia type iii who are closely followed up. Gut. 1991;32(10):1110–3.
237. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al. Management of precancerous conditions and lesions in the stomach (maps): guideline from the european society of gastrointestinal endoscopy (esge), european helicobacter study group (ehsg), european society of pathology (esp), and the sociedade Portuguesa de endoscopia digestiva (sped). Virchows Arch. 2012;460(1):19–46.
238. Hirota WK, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, et al. Asge guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper gi tract. Gastrointest Endosc. 2006;63(4):570–80.
239. Rokkas T, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. The long-term impact of helicobacter pylori eradication on gastric histology: a systematic review and meta-analysis. Helicobacter. 2007;12(s2):32–8.
240. Pimanov SI, Makarenko EV, Voropaeva AV, Matveenko ME, Voropaev EV. Helicobacter pylori eradication improves gastric histology and decreases serum gastrin, pepsinogen i and pepsinogen ii levels in patients with duodenal ulcer. J Gastroenterol Hepatol. 2008;23(11):1666–71.
241. De Vries A, Kuipers E. Review article: Helicobacter pylori eradication for the prevention of gastric cancer. Aliment Pharmacol Ther. 2007;26(s2):25–35.
242. Greenberg ER, Anderson GL, Morgan DR, Torres J, Chey WD. Bravo LE, et al. 14-day triple, 5-day concomitant, and 10-day sequential therapies for helicobacter pylori infection in seven latin american sites: a randomised trial. Lancet. 2011;378(9790):507–14.
243. Morgan DR, Torres J, Sexton R, Herrero R, Salazar-Martínez E, Greenberg ER, et al. Risk of recurrent helicobacter pylori infection 1 year after initial eradication therapy in 7 latin american communities. JAMA. 2013;309(6):578–86.
244. Toyokawa T, Suwaki KI, Miyake Y, Nakatsu M, Ando M. Eradication of helicobacter pylori infection improved gastric mucosal atrophy and prevented progression of intestinal metaplasia, especially in the elderly population: a long-term prospective cohort study. J Gastroenterol Hepatol. 2010;25(3):544–7.
245. Yang H-B, Sheu B-S, Wang S-T, Cheng H-C, Chang W-L, Chen W-Y. *H. Pylori* eradication prevents the progression of gastric intestinal metaplasia in reflux esophagitis patients using long-term esomeprazole. Am J Gastroenterol. 2009;104(7):1642–9.
246. Correa P, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. J Natl Cancer Inst. 2000;92(23):1881–8.
247. Wong BC-Y, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA. 2004;291(2):187–94.
248. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can helicobacter pylori eradication treatment reduce the risk for gastric cancer? Ann Intern Med. 2009;151(2):121–8.
249. Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BC-Y. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2003;95(23):1784–91.
250. Tian W, Zhao Y, Liu S, Li X. Meta-analysis on the relationship between nonsteroidal anti-inflammatory drug use and gastric cancer. Eur J Cancer Prev. 2010;19(4):288–98.
251. Nardone G, Rocco A. Chemoprevention of gastric cancer: role of cox-2 inhibitors and other agents. Dig Dis. 2004;22(4):320–6.
252. Yang HB, Cheng HC, Sheu BS, Hung KH, Liou MF, Wu JJ. Chronic celecoxib users more often show regression of gastric intestinal metaplasia after helicobacter pylori eradication. Aliment Pharmacol Ther. 2007;25(4):455–61.
253. Zhang L-J, Wang S-Y, Huo X-H, Zhu Z-L, Chu J-K, Ma J-C, et al. Anti-helicobacter pylori therapy followed by celecoxib on progression of gastric precancerous lesions. World J Gastroenterol. 2009;15(22):2731–8.
254. Leung WK, Ng EK, Chan FK, Chan WY, Chan K-F, Auyeung AC, et al. Effects of long-term rofecoxib on gastric intestinal metaplasia: results of a randomized controlled trial. Clin Cancer Res. 2006;12(15):4766–72.

255. You W-C, Brown LM, Zhang L, Li J-Y, Jin M-L, Chang Y-S, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. J Natl Cancer Inst. 2006;98(14):974–83.
256. Plummer M, Vivas J, Lopez G, Bravo JC, Peraza S, Carillo E, et al. Chemoprevention of precancerous gastric lesions with antioxidant vitamin supplementation: a randomized trial in a high-risk population. J Natl Cancer Inst. 2007;99(2):137–46.
257. Rautalahti MT, Virtamo JR, Taylor PR, Heinonen OP, Albanes D, Haukka JK, et al. The effects of supplementation with α-tocopherol and β-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. Cancer. 1999;86(1):37–42.
258. Hayashi T, Ishiwatari H, Ihara H, Kawano Y, Takada K, Miyanishi K, et al. Suppressive effect of sulindac on branch duct-intraductal papillary mucinous neoplasms. J Gastroenterol. 2009;44(9):964–75.
259. Siveke JT, Einwächter H, Sipos B, Lubeseder-Martellato C, Klöppel G, Schmid RM. Concomitant pancreatic activation of krasg12d and tgfa results in cystic papillary neoplasms reminiscent of human ipmn. Cancer Cell. 2007;12(3):266–79.
260. Chadwick B, Willmore-Payne C, Tripp S, Layfield LJ, Hirschowitz S, Holden J. Histologic, immunohistochemical, and molecular classification of 52 ipmns of the pancreas. Appl Immunohistochem Mol Morphol. 2009;17(1):31–9.
261. Lipkin S, Lee J, Imagawa D, Hewitt SM, Tucker C, Zell JA, et al. Phase II a trial testing erlotinib as an intervention against intraductal pancreatic mucinous neoplasms. Cancer Prev Res. 2011;4(4):512–3.
262. Sahasrabuddhe VV, Gunja MZ, Graubard BI, Trabert B, Schwartz LM, Park Y, et al. Nonsteroidal anti-inflammatory drug use, chronic liver disease, and hepatocellular carcinoma. J Natl Cancer Inst. 2012;104(23):1808–14.
263. Lu SC. S-adenosylmethionine. Int J Biochem Cell Biol. 2000;32(4):391–5.
264. Lu SC, Mato JM. S-adenosylmethionine in liver health, injury, and cancer. Physiol Rev. 2012;92(4):1515–42.
265. Ghoshal AK, Farber E. The induction of liver cancer by dietary deficiency of choline and methionine without added carcinogens. Carcinogenesis. 1984;5(10):1367–70.
266. Lombardi B. The choline-devoid diet model of hepatocarcinogenesis in the rat. Chemi carcinogenesis Springer. 1988:563–81.
267. Wainfan E, Poirier LA. Methyl groups in carcinogenesis: effects on DNA methylation and gene expression. Cancer Res. 1992;52(7 Supplement):2071s–7s.
268. Pascale RM, Simile MM, De Miglio MR, Feo F. Chemoprevention of hepatocarcinogenesis: S-adenosyl-l-methionine. Alcohol. 2002;27(3):193–8.
269. Simile MM, Saviozzi M, De Miglio MR, Muroni MR, Nufris A, Pascale RM, et al. Persistent chemopreventive effect of s-adenosyl-l-methionine on the development of liver puptative preneoplastic lesions induced by thiobenzamide in diethylnitrosamine-initiated rats. Carcinogenesis. 1996;17(7):1533–7.
270. Morgan TR, Osann K, Bottiglieri T, Pimstone N, Hoefs JC, Hu K-Q, et al. A phase ii randomized, controlled trial of s-adenosylmethionine in reducing serum α-fetoprotein in patients with hepatitis c cirrhosis and elevated afp. Cancer Prev Res. 2015;8(9):864–72.
271. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis c virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158(5_Part_1):329–37.

The Expanding Role of Endoscopy in Tissue Acquisition and Therapeutic Interventions for Gastrointestinal and Neuroendocrine Malignancies

30

James J. Farrell

Introduction

Since the development of the flexible fiberoptic endoscopy by Basil Hirschowitz and Larry Curtiss in 1958, gastrointestinal endoscopy has developed an established and important role in the diagnosis and treatment of patients with gastrointestinal and neuroendocrine malignancies [1]. The last 10 years has seen an accelerated expansion in its role in several areas of both tissue acquisition and therapeutic intervention related to both gastrointestinal and neuroendocrine malignancies. This chapter will focus on several of these new important developments including endoscopic ultrasound (EUS)-guided fine needle biopsy (FNB), endoscopic mucosal resection and endoscopic submucosal dissection, endoscopic ablative therapies, EUS-guided biliary access, and natural orifice transgastric endoscopic surgery (NOTES).

Tissue Acquisition

Optical Biopsy

Although the acquisition of intact tissue or cells for microscopic evaluation remains the gold standard in the diagnostic work-up of gastrointestinal malignancy, the combination of endoscopy and microscopy gives the possibility of on-site real-time evaluation. Confocal laser endoscopy (CLE) provides in vivo histology, either through using a dedicated endoscope or a through the endoscope probe [2]. With over a 1000-fold magnification of in vivo tissue, CLE can only cover a limited field within the mucosa, requiring extensive scanning to obtain an image of the larger gastrointestinal organ of interest. As a result, CLE is more useful to focus on relatively small areas, to assist in performing targeting endoscopic biopsy, to correctly identify and image lesion margins, and to follow up treatment response [3]. CLE is able to distinguish between normal, nonneoplastic (e.g., inflammatory), and neoplastic tissues with very high accuracy, resulting in it having a role in dysplasia surveillance in patients with premalignant diseases of the gastrointestinal tracts such as ulcerative colitis and Barrett's esophagus (BE) [4]. However, the procedure is time-consuming, requires the administration of a fluorescein, and raises the issue of the endoscopist making a histological diagnosis in the absence of a trained pathologist [3].

Endoscopic Ultrasound-Guided Fine Needle Aspiration and Fine Needle Biopsy

Endoscopic Ultrasound: Fine Needle Aspiration

Whereas EUS imaging alone has an established diagnostic role in the diagnosis of small lesions such as pancreaticobiliary tumors, as well as the luminal stage of esophageal, gastric, and rectal cancers, its major diagnostic strength is in its ability to safely and easily biopsy organs outside the lumen, including the pancreas, liver, lymph nodes, adrenal glands, and kidneys. Probably the most studied and utilized by EUS is EUS-FNA (fine needle aspiration) and more recently EUS-FNB (fine needle biopsy) of the pancreas, especially for both pancreatic ductal adenocarcinoma and pancreatic neuroendocrine neoplasms [5].

EUS-FNA refers to techniques used to acquire tissue primarily for cytologic evaluation, and EUS-FNB refers to techniques used to acquire tissue for histologic evaluation. Both are performed using a linear echoendoscope. Typically for pancreatic biopsy, the linear echoendoscope needs to be positioned in the 2nd and 3rd portion of the duodenum to biopsy uncinate lesions, the 2nd portion and the duodenal bulb for pancreatic head and neck lesions, and in the stomach for pancreatic neck, body, and tail lesions. Apposition between the linear echoendoscope and either the gastric or duodenal wall is necessary with

J. J. Farrell (✉)
Yale Center for Pancreatic Disease, Interventional Endoscopy, Section of Digestive Disease, Yale University School of Medicine, New Haven, CT, USA
e-mail: james.j.farrell@yale.edu

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_30

continuous endoscopic suction to decrease the amount of air intervening and so improve the EUS imaging. Under direct EUS guidance, a needle may be passed into the target lesion within the pancreas, with fanning recommended through at least four different areas to sample most pancreatic masses [6, 7]. A variety of different gauge needles are available for EUS-FNA ranging in size from 25 to 19 gauge, although most endosonographers use either a 25G or 22G needle. It is felt that the smaller needle is more easily passed through desmoplastic tissue seen with pancreatic ductal adenocarcinoma and induces less bleeding, but it is unclear if there are significant differences in tissue yield between both needles.

Whereas EUS imaging is very sensitive to diagnose pancreatic malignancy (about 95%), it is not specific. Prior to the advent of EUS, pancreatic cancer tissue diagnosis was done at the time of surgical exploration, by bile duct brushings through endoscopic retrograde cholangiopancreatography (ERCP) or by percutaneous biopsy using either abdominal ultrasound guidance or computed tomography (CT) guidance. ERCP brushing biopsy has a sensitivity of 20–71% in the diagnosis of pancreatic malignancy [8]. However, EUS-FNA has now typically replaced these methods as the test of choice for primary pancreatic tissue diagnosis [5]. Meta-analyses have shown a pooled sensitivity of between 85% and 87% and a specificity of 96–98% for EUS-FNA in diagnosing pancreatic cancer [9, 10].

The recognized benefits of EUS-FNA in the evaluation of pancreatic masses include its high yield compared with alternative methods of diagnosis, the ability to detect small lesions, a low risk of seeding, and the overall cost-effectiveness. Although no definitive randomized clinical trial (RCT) data exist, EUS-FNA does appear to be effective after nondiagnostic CT-guided biopsy or ERCP with cytologic brushing [11, 12]. The theoretical benefit of EUS in detecting and so biopsying small pancreatic masses has been borne out by several large studies showing the superior accuracy of EUS-FNA compared with either CT-FNA or abdominal ultrasound FNA for pancreatic masses less than 3 cm (86% vs. 62%) and even for masses not seen on multidetector CT [13, 14]. There appear to be a decreased risk and clinical significance of peritoneal seeding associated with EUS-FNA compared with percutaneous biopsy in patients with pancreas masses (2.2% vs. 16.3%) [15]. Overall, EUS-FNA of pancreatic masses is considered very safe with an overall pancreatitis risk rate (0.3–0.9%) and overall complication rate of 2.5%. These are compared with high rates of pancreatitis of up to 4% with percutaneous biopsies and between 5% and 15% for ERCP-guided biopsies [16, 17]. Diagnostic EUS-FNA biopsy of the pancreas has been shown to result in less invasive additional procedures and more cost-effective management of pancreatic cancer, especially by avoiding unnecessary surgeries [18, 19].

Nevertheless, EUS-FNA remains operator-dependent with a very significant learning curve, requiring specialized training beyond general endoscopy training [20]. Sampling error due to pancreatic cancer desmoplastic reaction and necrosis, especially in more aggressive tumors, is associated with the suboptimal performance of EUS-FNA. The use of rapid on-site cytology evaluation (ROSE), whereby pathologists present during the EUS-FNA procedure advise the endoscopist about adequacy and diagnosis, results in improved overall accuracy, fewer needle passes necessary to make a definite diagnosis, and decreased need for repeat diagnostic procedures [21, 22]. Several studies have shown a decreased sensitivity of EUS in identification of pancreatic malignant masses in the setting of chronic pancreatitis due to the difficulty in distinguishing the mass from the surrounding abnormal pancreatic parenchyma [22]. In addition, EUS-FNA has a lower sensitivity of diagnosing malignancy (ranging between 53% and 71%) in the setting of chronic pancreatitis even with the use of additional needle passes and the presence of an on-site cytologist [23, 24]. Although initial studies seemed to suggest the inferior diagnostic yields of EUS and EUS-FNA in the diagnosis of other nonadenocarcinoma lesions of the pancreas such as pancreatic neuroendocrine tumors (PNETs), lymphomas, or metastatic lesions to the pancreas, most recent work seems to suggest a higher sensitivity comparable to that seen in pancreatic ductal adenocarcinoma probably related to the use of ROSE and special cytologic stains [25].

Endoscopic Ultrasound: Fine Needle Biopsy

The current diagnostic yield for EUS-FNA cytology of pancreatic masses is high better than for non-pancreatic indications, but not perfect [26–30]. There are several reasons for the suboptimal diagnostic results, including variable operator-dependent EUS imaging and technique, the lack of locally available cytologic expertise, poor specimen cellularity, and lack of detail on the tissue architecture and morphology. This latter issue is particularly problematic for distinguishing well-differentiated pancreatic ductal adenocarcinoma from normal pancreatic tissue, as well as trying to diagnose pancreatic malignancy in the setting of chronic pancreatitis [23, 31]. Often there is an insufficient amount of tissue with EUS-FNA for additional ancillary studies, leading to lack of a definitive diagnosis and the need for repeat tissue acquisition.

Hypocellular biopsy tissue material is a common cause for a false-negative diagnosis. Hence there are several theoretical benefits to endoscopically pursuing a pancreatic histology or core biopsy (EUS-FNB). Firstly, the ability to assess tissue architecture may improve the ability to diagnose well-differentiated pancreatic adenocarcinoma, where the cytologic findings (lack of the typical hyperchromasia of malignancy, minimal architectural disorder, and modestly increased nuclear-cytoplasmic ratios) may be similar to normal-appearing pancreas, and in diagnosing malignancy in the setting of chronic pancreatitis. The second reason to consider a core biopsy for histology is the need to get a more representative sample of the pancreatic mass. For example, because of

the dense stromal proliferation typically seen in pancreatic ductal adenocarcinoma, it is possible that core histologic tissue would allow for further study of the stroma, which is typically not commented on or assessed during regular pancreas FNA cytology. Another reason to pursue histologic tissue is to allow for immunohistochemistry or additional marker studies. With our increased understanding of the molecular basis for pancreatic disease and the role in which molecular markers (protein, DNA, or RNA based) may be helpful in making a diagnosis—such as separating primary pancreatic ductal adenocarcinoma from similar looking metastases to the pancreas or even predicting a response to treatment—there is a need for greater volumes of tissue that can be processed in the appropriate way to study and quantify these markers. While this may be possible with cytology, the specimens are typically small, and quantitation of immunocytochemistry markers is difficult if there is a limited cytologic specimen. A histologic core of tissue allows the pathologist to obtain several sections for immunohistochemistry protein analysis and possibly quantitate the tissue-based marker used. Under these circumstances both stroma and epithelial markers may be assessed [32, 33]. In addition, the ability to microdissect out epithelial tissue may facilitate more accurate DNA or RNA analysis of the pancreatic specimen, by being able to identify the cell-based origin of the marker in question [34]. Finally, it is possible that, with the known limitation of EUS-FNA cytology, the availability of reliable pancreatic histologic biopsy and core biopsy may remove the need for on-site cytologic evaluation and multiple FNA needle passes.

A variety of additional strategies exist to overcome the current limitation of both EUS and EUS-FNA or FNB. Contrast-enhanced EUS and EUS elastography are two new supplemental imaging technologies, which may improve diagnostic yield of EUS imaging and help target EUS-FNA and FNB more precisely. Contrast-enhanced EUS employs oscillation of microbubbles using ultrasound waves after injection of intravenous contrast containing microbubbles to enhance imaging of lesions associated with hypervascular structures such as endocrine neoplasms. EUS elastography uses assessment of tissue stiffness to help differentiate between malignant and nonmalignant masses [35]. In addition, a variety of molecular markers including immunocytochemical markers, fluorescence in situ hybridization (FISH) analysis, DNA mutational analysis including whole exome sequencing, and micro-RNA analysis have been proposed to improve the diagnostic yield of EUS-FNA cytology, but currently most are not in routine clinical use [36].

Cholangioscopy- and Pancreatoscopy-Guided Biopsies

The increasing availability of reliable high-quality ERCP-guided cholangioscopy and pancreatoscopy, which allows for direct visualization of the biliary tree and pancreatic duct, respectively, has increased the role for diagnostic ERCP [37]. For indeterminate biliary strictures (those without an associated pancreatic or other mass on imaging), where the differential may include a pancreaticobiliary malignancy such as cholangiocarcinoma or pancreatic cancer, cholangioscopy-targeted biopsies have an increased diagnostic yield. Although typically not performed during the routine evaluation of pancreatic cancer, ERCP-guided pancreatoscopy may have a role in the diagnosis and staging of a premalignant pancreatic main duct lesion such as intraductal papillary mucinous neoplasms (IPMN). The direct visualization and biopsy of papillary fronds associated with this disease can be helpful in confirming the diagnosis.

Biopsy of Gastrointestinal Subepithelial Lesions

Gastrointestinal subepithelial lesions represent a broad collection of pathologies of the gastrointestinal tract including leiomyomas, gastrointestinal stromal tumors (GISTs), lipomas, and granular cell tumors. Routine endoscopic biopsy and even EUS-guided FNA or FNB are often insufficient to make a tissue diagnosis. This is further complicated by a need for a large amount of histologic quality tissue for additional immunohistochemistry. A variety of newer endoscopic tissue acquisition techniques have been described to address these issues specifically.

Single-incision needle knife (SINK) biopsy has been proposed as a routine method for tissue acquisition for these subepithelial lesions [38]. After EUS for evaluation of the subepithelial lesion, a 6- to 12-mm linear incision using a needle knife is made followed by regular forceps bites through this incision to obtain three to five regular endoscopic biopsy bites for histology. Compared with the often low diagnostic yield of EUS-FNA (approximately 12% for subepithelial lesions), SINK biopsy has a reported diagnostic rate up to 93%. Another technique to diagnose and possibly treat small subepithelial lesions of the gastrointestinal tract includes suctioning of the lesion into a cap, ligation below the tumor, unroofing of the mucosa overlying the subepithelial tumor with a needle knife, and biopsying from exposed tumor.

Therapeutic Interventions

Endoscopic Resection: Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection

Endoscopic resection of mucosal and submucosal dysplastic and cancerous gastrointestinal lesions is increasingly an alternative therapeutic (and often diagnostic) option to surgical management [39]. Specific areas where endoscopic

resection has an established role include in the esophagus (dysplasia in the setting of Barrett's esophagus, superficial esophageal adenocarcinoma, and squamous cell carcinoma), the stomach (gastric dysplasia, early gastric cancer, and carcinoid), small bowel (duodenal adenoma and ampullary adenoma) as well as in the colon (adenomatous polyps, some early colorectal cancers, and certain carcinoids).

Technique

Although a variety of endoscopic resection techniques exist, the two main types are either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) [39]. EMR involves snare resection without or with prior suction and lifting of the target lesion (Fig. 30.1). ESD involves dedicated tools and skilled endoscopic submucosal dissection to remove (dissect) lesions off the submucosa (Fig. 30.2). Most studies comparing ESD with EMR suggest that ESD is associated with improved outcomes including higher en bloc and curative resection rates in addition to lower rates of local recurrence for malignant and premalignant lesions of the gastrointestinal tract, especially in the areas of early gastric cancer, esophageal squamous cell carcinoma, and esophageal adenocarcinoma.

Endoscopic mucosal resection is typically performed using two techniques: suction (suck-and-cut) and non-suction (lift-and-cut) techniques. Submucosal injection with an injection needle prior to resection is used to separate mucosal and submucosal lesions from the muscularis propria and so decrease the risk of perforation. Lack of a lift of the lesion after submucosal injection or puckering is concerning for deeper invasion of the neoplastic lesion into the muscularis propria but can also be seen with scarring from prior endoscopic biopsy and resection. It is often taken as an indication not to proceed with endoscopic resection.

Submucosal injections are performed using an injection needle at one or multiple sites adjacent to the lesion in an attempt to lift the lesion away from the muscularis propria. Normal saline is the most commonly available substance for submucosal injection but can be absorbed out of the submucosa quickly, thereby decreasing its effect. Hence the use of more hypertonic solution, such as hypertonic saline, 50% dextrose, 10% glycerol, or sodium hyaluronate, has all been employed to maintain the submucosal fluid cushion longer, especially for endoscopic submucosal dissection [40]. For example, 50% dextrose has been suggested to be superior to normal saline for prolonged submucosal fluid cushion (SFC), lasting up to 5 minutes [41, 42].

After submucosa injection and lifting the lesion away from the muscularis propria, the lift-and-suction technique uses a transparent cap affixed to the tip of the endoscope (cap-assisted EMR, EMRC) to suction the lesion of interest into the cap, after which it is resected using a snare placed through the cap or after application of a band similar to a variceal ligation band [43, 44]. For the technique using a band, resection is performed using a snare placed through the endoscope above or preferably below the applied band [43]. Non-suction EMR techniques also exist, including using a grasping device to pull the lesion away from the muscularis propria, after which a snare is used to resect the specimen. Whereas EMR has typically been used for small lesions <2 cm with the plan to achieve an en bloc resection and confirm tissue resection pathologically, the concept of widespread piecemeal EMR may have a role to remove large areas, for example, of high-grade dysplasia (HGD) in Barrett's esophagus [45]. However, it can be associated with an increased stricture formation when involving the entire esophageal circumference.

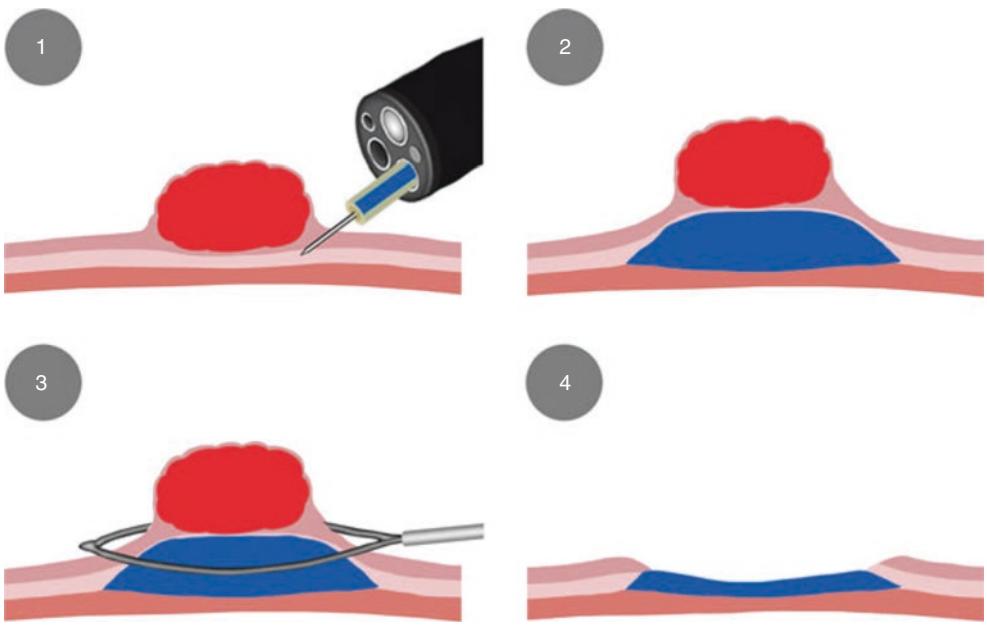


Fig. 30.1 The steps of an injection-assisted EMR: (1) An injection needle is advanced into the submucosal plane. (2) A submucosal bleb is created, which protects the muscularis propria from thermal injury. (3) A snare is passed over the lesion. (4) A snare polypectomy is completed. (Reprinted with permission from Samdani et al. [157])

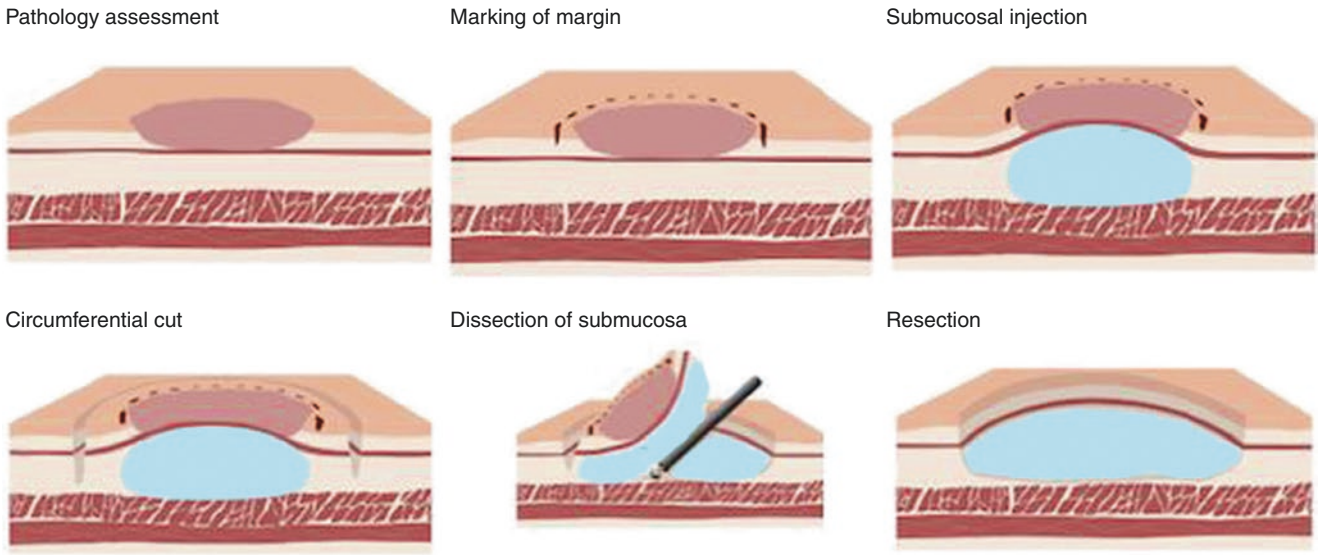


Fig. 30.2 Schematic description of ESD. (Reprinted with permission from Hammad et al. [158])

Endoscopic submucosal dissection uses a modified needle knife to remove the lesion by dissecting through the submucosa, again after submucosal injection of fluid [46]. It may remove mucosal and submucosal tumors en bloc irrespective of size of the lesion. While pioneered in Japan, there is now a growing experience in North America and the rest of the world with this technique in the management of early neoplasia of the gastrointestinal tract, especially gastric cancer.

Prior to performing ESD, the lesion and the margin may be imaged more closely using narrow band imaging (NBI) or chromoendoscopy, and the outer margin of the lesion may be marked with cautery or argon plasma coagulation. After submucosal injection is performed under the markings, a circumferential incision guided by the markings is performed with the ESD knife, creating a mucosal flap and access for submucosal dissection. The submucosal dissection to remove the attached mucosal dissection is technically challenging, requiring avoidance or treatment of bleeding submucosal vessels, as well as avoiding the muscularis propria in the dissection plane to avoid full-thickness perforation. The performance of ESD requires specialized tools and advanced endoscopic training and experience; and a variety of adverse events including perforation, bleeding, and incomplete removal of the tumor have all been described [47]. A hybrid technique, which starts with an endoscopic submucosal dissection technique of marking and incising the lesion per ESD, and then finishes with EMR snare resection of the lesion, has been described [48]. The benefit of this approach include en bloc resection of lesion permitted by standard EMR with less of the complexity and complications associated with submucosal dissection.

Adverse Events

Overall, endoscopic resection is a safe procedure that may be performed on outpatients. Reported adverse events in the esophagus include stricture formation, bleeding, and perforations [49, 50]. In the esophagus, the early complication of perforation, which often presents with mediastinal emphysema, is reported in up to 3%. Typically, these have been managed without surgery but may require management of pneumathoraces. Immediate bleeding has been reported in up to 10% of patients and can typically be treated endoscopically. Late complications of endoscopic resection include esophageal stricture development, often associated with circumferential EMR and ESD, which may be treated successfully with endoscopic dilatation. Steroid injection at the time of endoscopic resection may decrease the risk of stricture formation. Other late bleeding complications (defined as occurring after 5 days) have also been reported in series in up to 1% of patients.

In stomach EMR, immediate bleeding has been reported in up to 30% of cases, with delayed bleeding being reported in up to 5% of patients [51]. For ESD, the reported rates of early bleeding and late bleeding are <3%, with the size of the resected lesion (>4 cm) and the use of anti-thrombotic medication being risk factors associated with bleeding [52]. Most forms of gastric bleeding related to endoscopic resection may be managed endoscopically. Perforation is more common with gastric ESD compared with EMR, with one meta-analysis reporting a rate of 4.5%, compared with 1.0% [53]. Treatment of a perforation generally requires open or laparoscopic surgery, although endoscopic clipping, use of an over-the-scope clip device, and even endoscopic suturing have been described in the management of small perforations [54]. Factors associated with an increased risk of perforation with ESD include upper stomach tumor location and tumor size >20 mm.

Similar adverse events are also reported in the colon including bleeding (up to 24%), perforation, and post-endoscopic submucosal dissection electrocoagulation syndrome [51]. Perforations have been reported in up to 10% of patients undergoing ESD for colorectal neoplasms. Although they can frequently be managed by endoscopic clipping and conservative treatment, surgery is still required in some cases. Post-endoscopic submucosal dissection electrocoagulation syndrome, which has been reported in up to 40% of cases, develops when electrical current applied during the procedure extends past the mucosa into the muscularis propria and serosa, resulting in a transmural burn without perforation [55]. Symptoms include fever, rebound tenderness, and marked leukocytosis. It is associated with lesions larger than 3 cm and location in the rectosigmoid.

Technical and Clinical Outcomes

Esophageal endoscopic resection is frequently indicated for both the diagnosis and therapy of both early cancer and high-grade dysplasia, especially in the setting of Barrett's esophagus [56–59]. For patients with esophageal cancer or high-grade dysplasia, endoscopic resection is often used in conjunction with an endoscopic ablative technique such as radiofrequency ablation (RFA) after the initial endoscopic resection to manage the field defect. From a diagnostic perspective, when adenocarcinoma or HGD is confined to the mucosa at the time of endoscopic resection, then that may be sufficient treatment. However, if invasion into the submucosa is identified, then other treatment options should be considered given the high rate of nodal metastases (up to 17%). Whereas endoscopic submucosal dissection can achieve a large en bloc resection, standard EMR technique is useful for lesions <2 cm in diameter, involving less than one-third of the circumference of the esophageal wall and are limited to the mucosa of the esophagus, which may be assessed prior to resection with EUS or after endoscopic resection by pathology review of the margins of the resection specimen [60].

For preneoplastic conditions of the esophagus such as Barrett's esophagus, endoscopic mucosal resection is associated with high rates of complete eradication of intestinal metaplasia (59–100%) and dysplasia (86–100%) [61, 62]. Complete eradication of HGD or early adenocarcinoma was achieved in up to 97% of patients with EMR in one study, of which up to 22% of patients had a recurrence requiring addition of endoscopic treatment in up to 85% of patients before complete remission was achieved. Risk factors associated with recurrence after EMR included piecemeal resection, long-segment BE, no mucosal ablative therapies of BE after complete remission, a lengthy time (longer than 10 months) to achieve complete remission, and multifocal neoplasia [58].

There are low mortality rates following endoscopic resection of esophageal cancer and high-grade dysplasia, with 5-year survival rates ranging from 76% to 100%. However, survival is lower in patients with multiple or circumferential lesions or with lesions that extend beyond the lamina propria [61, 63, 64]. Recurrences are seen in between 3% and 32% of patients and can often be treated with additional local endoscopic therapy [61, 63, 64]. Compared with equally matched early stage esophageal cancer (T1[a and b]) who had undergone surgery, patients treated endoscopically had higher 30-day survival rates than those treated surgically, but 5-year survival was still lower in the endoscopically treated group than in the surgery group (77% vs. 88%), possibly related to the endoscopic management of T1b tumors, which are associated with a higher risk of lymph node involvement [60].

Factors favoring selection of patients with early gastric cancer who are appropriate for endoscopic resection with EMR or ESD include high probability of en bloc resection, tumor histology (intestinal-type adenocarcinoma, tumor confined to the mucosa, and absence of venous or lymphatic invasion), and tumor size and morphology (<20 mm in diameter, without ulceration, and <10 mm in diameter if flat or mildly depressed) [65–68]. Proposed "expanded criteria" for endoscopic resection of intestinal-type early gastric cancer include mucosal tumors of any size without ulceration, mucosal tumors <30 mm with ulceration, and submucosal tumors <30 mm confined to the upper 0.5 mm of the submucosa without lymphovascular invasion [68]. Patients meeting the "expanded criteria" are at lower risk of lymph node metastases than those who do not meet them, although patients meeting "expanded criteria" are at an increased risk of lymph node metastases compared with those who meet standard criteria (2% vs. 4%). For patients who meet these "expanded criteria," and wish to avoid surgery, removal of the tumor using ESD (rather than EMR) is generally preferred because ESD is able to achieve a deeper resection margin and en bloc resection [68]. The general indications for gastrectomy with removal of perigastric lymph nodes include the low probability of en bloc resection with EMR or ESD (i.e., the endoscopic resection would be piecemeal), diffuse rather than intestinal-type adenocarcinoma pathology, submucosal tumor size >30 mm, or an ulcerated tumor, or evidence of lymphovascular (lymphatic or venous) invasion in the primary tumor, or known/suspected regional lymph node metastases.

A large meta-analysis of Japanese studies with 1852 patients shows complete resection is possible in more than 70% of patients, with recurrent cancer seen in only 3% and a very high disease-specific survival of 99% [69]. Due to differences in how Japanese and non-Japanese pathologists classify early gastric cancer and high-grade dysplasia, it is unclear if these very positive results may be achieved outside

of Japan [70]. Due to the high risk of piecemeal resection with EMR being associated with higher rates of local recurrence, ESD is now an attractive management option for these lesion as it permits en bloc resection of larger tumors that can be treated with EMR and also permits a deeper resection margin in patients with submucosal involvement who are candidates for endoscopic resection. Complete resection rates appear to be higher with ESD (83%) than with EMR (24%) when comparing equivalent-sized lesions, with on average more EMR lesions being removed piecemeal compared with ESD (58% vs. 83%) [71].

Local recurrences occur after gastric endoscopic resection, especially associated with incomplete resections (up to 5%). The management of incomplete resection after either gastric EMR or ESD is still controversial, as not all patients with tumor-positive resection margins will have residual tumor or tumor recurrence. The inability to often properly assess the resection margin (both lateral and deep), especially for patients who have undergone piecemeal resection (who are under increased risk of recurrence), makes further decision-making difficult. Typically, gastrectomy has been recommended for patients with incomplete resections, especially for tumors with positive margins, whereas for poor surgical candidates, those with submucosal involvement or lymphovascular invasion may be considered for repeat endoscopic resection. Often additional local ablation treatments endoscopically are necessary to achieve complete eradication for patients with incomplete resection.

Patients with early gastric cancer who undergo EMR have a high rate of successful eradication of cancer (70–85%), with 5-year survival rates of 84–86% [72, 73]. These rates are similar to surgical gastrectomy outcomes. The disease-specific survival rates at both 5- and 10-year follow-up have been reported as high as 99%. The complete endoscopic resection rate was lower (approximately 50%) with flat elevated lesions larger than 2 cm and with flat depressed lesions that were either larger than 1 cm or were associated with undifferentiated adenocarcinoma [72, 73].

There are no randomized trials comparing endoscopic versus surgical management of early gastric cancer, although studies comparing outcomes in patients treated with endoscopic resection with those treated with gastrectomy suggest similar clinical outcomes [74, 75]. There were no differences between the treatments with regard to mortality, recurrence rates, or complications. However, patients treated with EMR had a higher risk of metachronous gastric cancer, a shorter median hospital stay (8 vs. 15 days), and lower costs of care. The role of adjuvant therapy (e.g., chemotherapy or radiation therapy) for patients who have undergone complete endoscopic resection of early gastric cancer is not clearly established, especially for patients with node-negative disease. Although there are no clear guidelines, the treatment options in patients who develop recurrent early gastric cancer include surgery and repeat attempts at endoscopic resection (typically endoscopic submucosal dissection) [76].

Colorectal endoscopic resection can be used in the treatment of colorectal cancers, including adenocarcinoma and rectal carcinoid tumors [77]. Standard traditional inject-and-cut methods of EMR for colonic neoplasms are reported with complete en bloc removal rates of 86–97%. Factors associated with incomplete removal include size >2 cm and a large sessile configuration. A wide variety of sizes and shapes of colonic neoplasms are amenable to EMR. However, depressed lesions that may have invasion into the submucosa, even when they are small, and deep invasion (e.g., lesion fails to lift after injection with saline into the submucosa) are a contraindication to EMR, due to the high risk of perforation. ESD is also used in the treatment of colon polyps and cancers. In a meta-analysis of studies of patients undergoing ESD for large colonic polyps, successful en bloc polyp resection (including histologically negative margins for adenoma) was achieved in 75–89% of procedures [76].

Outcomes following EMR in the colon are good, particularly if the lesion can be removed en bloc. In a large meta-analysis of both adenomas and early carcinomas (mucosal invasion or submucosal invasion <1 mm) removed using EMR, there was a 15% rate of recurrence especially following piecemeal resection compared 3% with en bloc resection [76, 78]. Retreatment at follow-up endoscopy is associated with a recurrence rate of 21%. The 3-year survival rate for patients treated endoscopically is reported at 100%. Long-term outcome studies in patients who undergo ESD for the treatment of colonic lesions suggest good long-term outcomes for patients with low-risk colon lesions that are completely removed with ESD [79, 80]. Outcomes are not as good for patients with rectal lesions or lesions with high-risk features. In one large study of colonic ESD, low-risk lesions (completely resected, were well- or moderately differentiated adenocarcinoma, lacked vascular invasion, and had a depth of submucosal invasion <1 mm) were associated with recurrence rates of 0% and 6.3% for colon and rectal cancers, respectively, and 5-year recurrence-free survival rates were 96% and 90%, respectively. For those with high-risk lesions (all other lesions) treated with ESD, the recurrence rates were 1.4% and 16%, respectively, with 5-year recurrence-free survival rates of 96% and 77%, respectively. Among those with high-risk lesions who underwent surgery, the recurrence rates were 1.9% and 4.5%, respectively, with 5-year recurrence-free survival rates of 97% and 95%, respectively [79]. EMR has also been evaluated in patients with rectal carcinoids with good success rates, with one large study quoting a complete resection rate of 88% for lesions 20 mm or less in diameter [81].

Endoscopic Management of Gastrointestinal Subepithelial Tumors

ESD has also been used in the treatment of gastric subepithelial tumors, such as gastrointestinal stromal tumors and leiomyomas, with high rates for en bloc complete resection including negative margins ranging up to 80% [82, 83]. Not surprisingly, higher rates of resection are associated with tumors in the submucosa compared with those arising from the muscularis propria with no rates of recurrence for those who had complete resection with negative margins [82, 83].

The development of peroral endoscopic myotomy (POEM) relies on the submucosal tunneling technique. Using this technique it is possible to remove submucosal tumors arising from the muscularis propria such as leiomyomas or gastrointestinal stromal tumors in the esophagus or at the esophagogastric (EG) junction, with a high (86–100%) successful en bloc resection (negative lateral and deep tumor-free margins in all cases) and no local recurrence or distant metastases during 12-month follow-up [84]. However, the significant complication rate (pneumothorax subcutaneous/mediastinal air and pneumoperitoneum) has been reported as high as 35%. These are typically long procedures with a mean procedure time of up to 1 hour being reported [85].

Endoscopic full-thickness resection (EFTR) is another novel method to resect submucosal tumors, which traditionally have been managed using surgical resection. It consists of resecting the tumor without interrupting the tumor capsule and with active perforation. At the end, the defect will close with a suture allowing the endoscopic closure of colonic wall mucosal defect. A prospective pilot study has shown the feasibility and safety of EFTR of colonic SMTs combined with standard metallic clips. Newly developed endoscopic clipping and sewing devices, such as the over-the-scope clip (OTSC; Ovesco AG, Germany) and the OverStitch™ suturing device (Apollo Endosurgery, Inc., Austin, Texas), should increase the safety of the colonic EFTR procedure but need further investigation.

Endoscopic Ablation

Several endoscopic ablative technologies exist including multipolar electrocoagulation, argon plasma coagulation (APC), photodynamic therapy, radiofrequency ablation, and more recently cryoablation. The most widely studied is RF ablation, especially in the setting of dysplastic Barrett's esophagus.

Radiofrequency Ablation

Typically, a balloon-based catheter can be used to circumferentially ablate Barrett's esophagus, or a paddle-based catheter can be used for focal ablation of short segments of Barrett's esophagus, mucosal tongues, and residual islands of dysplasia. EMR alone removes a focal area from the Barrett's esophagus, with the patient remaining at risk for developing metachronous lesions arising from the residual Barrett's mucosa. Hence, the addition of an ablative therapy with EMR decreases this risk. However, flat dysplasia in the setting of Barrett's esophagus can be ablated with RFA alone.

A multicenter randomized, sham-controlled trial investigated the efficacy of RFA in eradicating Barrett dysplasia and preventing progression of disease in 127 patients, 64 with low-grade dysplasia (LGD) and 63 with HGD [86]. Complete eradication of dysplasia was achieved in 86% of patients, with no statistically significant difference between the LGD and HGD groups. By contrast, the sham treatment arm had LGD eradication of 23% and HGD eradication of 19%. A systematic review, involving 9 studies and more than 429 patients, found that the reported complete eradication rate for Barrett dysplasia and metaplasia was between 71–100% and 46–100%, respectively, without any serious adverse events being reported [87]. Although long-term follow-up studies are still limited, the 5-year follow-up data suggest that eradication of the Barrett's mucosa is maintained in more than 90% of patients. Buried glands, whereby Barrett's epithelium may be "buried" beneath neosquamous after treatment, were noted only in one case [88]. A more recent multicenter prospective trial, conducted in Europe, showed excellent results in terms of eradication of HGD and early cancer in Barrett's esophagus when a combined approach of endoscopic resection and RFA was used [89].

The risk of malignant progression associated with BE and LGD is controversial, with variable rates of neoplastic progression, with progression to high-grade dysplasia and invasive cancer reported as high as 27% after 2 years of follow-up. Hence the role of RF ablation for the management of BE with LGD is controversial. A multicenter randomized trial comparing RFA with surveillance in patients with Barrett's esophagus and LGD found that RFA resulted in a reduced risk of neoplastic progression in a 3-year follow-up period [90]. The role of RFA in patients with non-dysplastic BE is also highly controversial. An argument against RFA in these patients is that the annual risk of malignant progression is low and many patients with BE are older adults with significant comorbid medical conditions that may affect their overall survival and quality of life. Factors that favor treatment include the efficacy and safety profile of RFA and potential cost savings. For most patients with non-dysplastic BE, the overall health benefit of RFA may be too low to currently indicate its use.

Patients who undergo RFA for BE are at low risk of subsequently developing esophageal adenocarcinoma. In a registry study of 4982 patients who underwent RFA for BE followed for a mean of 2.7 years, esophageal adenocarci-

noma developed in 100 patients (2%; incidence of 7.8 per 1000 patient-years) [91]. Although the majority of cancers developed in patients with baseline HGD (83 patients), invasive cancer was also seen in patients with baseline LGD (12 patients) and non-dysplastic BE (3 patients). Factors associated with cancer development in BE after RFA included male sex, older age, longer BE segment length, and higher pathologic grade at baseline. The strongest predictors for developing esophageal cancer after RFA are the indication for treatment and the complete remission rates for dysplasia and intestinal metaplasia.

The role of RFA in treating squamous dysplasia and early SCCs is less well studied and had been associated with cure rates up to 84% at 12-month follow-up. A prospective cohort of patients with squamous dysplasia from the UK HALO registry showed only a modest 50% response to RFA [92].

Adverse events reported with esophageal radiofrequency ablation include esophageal strictures, upper gastrointestinal hemorrhage, and chest pain. Whereas stricture rates from non-RFA ablation techniques ranging from 0% to 56% have been described with other endoscopic ablation techniques, studies of RFA for Barrett's esophagus have shown lower rates of stricturing (0–6%). In a large meta-analysis of 18 studies of esophageal RFA, the most common adverse events were stricture formation (5%), pain (3%), and bleeding (1%) [87]. Risk factors for the development of esophageal strictures after RFA include prior endoscopic resection or a narrow esophagus at baseline due to underlying reflux disease. There also is concern that residual Barrett's esophagus could be hidden beneath the neosquamous epithelium following ablation, but the clinical relevance of "buried" Barrett's is still uncertain. The possibility of occult malignant progression of the buried glands has been suggested by cases of adenocarcinoma arising underneath neosquamous epithelium after ablation therapy with radiofrequency ablation, photodynamic therapy, or argon plasma coagulation.

Other gastrointestinal therapeutic applications for RFA include the biliary tree and pancreas. Typically, endoscopic palliation of malignant biliary obstruction includes placement of plastic stents or self-expandable metal stents (SEMSs). Endobiliary RFA has been used as primary therapy in unresectable biliary malignancies or to treat occluded uncovered biliary SEMSs because of tumor ingrowth, with a good efficacy and safety profile [93]. However, its survival benefit in this cohort of patients is unclear. Prior ablation of hilar cholangiocarcinoma with photodynamic therapy (PDT) did show a survival benefit [94]. However, its applicability is limited by costs, availability, photosensitivity, and the need for repeated treatment sessions. Nonrandomized historical cohort study data from small studies does suggest that endobiliary RFA may have a potential early survival benefit in patients with biliary obstruction secondary to unresectable pancreatic cancer [93]. However, another recent small retrospective study suggested that there is no survival benefit in patients with unresectable cholangiocarcinoma who undergo ERCP-directed RFA compared with ERCP-directed PDT for unresectable cholangiocarcinoma [95].

EUS-guided pancreatic indications for RFA are increasing [96]. The safety and efficacy of EUS-guided RFA of pancreatic cysts has been demonstrated in a small set of patients with pancreatic cystic neoplasms and neuroendocrine tumors. Using a 19- or 22-gauge needle, an RFA probe was passed through the needle and, under EUS guidance, used to treat several patients [97]. There was a decrease in cyst size (39 vs. 20 mm) after RFA and a change in vascularity or an area of necrosis in the neuroendocrine tumors, with a single complication of abdominal pain in one patient. Several EUS-guided ablative treatments for symptomatic pancreatic endocrine neoplasms have been reported including most recently EUS-guided RFA [96, 97].

Endoscopic Cryotherapy

For application in gastrointestinal oncology, cryotherapy can be performed using devices designed for use with endoscopes. During cryotherapy, a substance used to produce very low temperature is used to freeze the target tissue, and repeated freeze/thaw cycles result in the destruction of abnormal tissue. In endoscopic cryotherapy, the cryogen is typically a liquefied gas, such as nitrogen or carbon dioxide, which may be either directly applied to tissue or used within a balloon device. Endoscopic cryotherapy was first used for the treatment of Barrett's esophagus, and the indications for its use in other gastrointestinal cancer disorders are expanding [98].

A variety of different endoscopic cryotherapy ablation techniques have been assessed in Barrett's esophagus. In a prospective multicenter study with follow-up of 2 years, 80 patients with dysplastic BE completed endoscopic cryotherapy (liquid nitrogen spray) every 2–3 months until there was no endoscopic evidence of BE and no histologic evidence of dysplasia. Complete eradication of dysplasia and intestinal metaplasia (IM) was achieved in 84% and 64% of patients, respectively [99]. Long-term recurrence of intestinal metaplasia after cryoablation also has been studied in patients with both high-grade dysplasia and intramucosal cancer who initially attained complete eradication of intestinal metaplasia (CE-IM) with liquid nitrogen cryoablation. In follow-up of up to 4 years, recurrent IM and dysplasia were seen in 30–41% and 15–19% of patients, respectively [100, 101]. Endoscopic cryoablation may also have a role in the treatment of refractory or recurrent dysplasia after RFA failure, with complete eradication of dysplasia being achieved in 75% and CE-IM in 31% [102].

The ability of cryotherapy to treat into the deep submucosa makes it a useful treatment option for esophageal cancer. In a multicenter retrospective study, 79 patients with

esophageal cancer of a variety of stages from T1 to T4 (although the majority were T1 lesions) who either failed or were ineligible for conventional therapy underwent endoscopic cryotherapy with liquid nitrogen as a salvage therapy for local disease control. The majority of the patients had received previous therapies including EMR, photodynamic therapy, chemoradiation, argon plasma coagulation, RFA, or a combination of these therapies [103]. Of the 49 patients who completed cryotherapy, complete endoscopic remission was observed in 72% of the patients with T1 stage tumors compared with 33% of the patients with stage T2 to stage T4 disease. Overall, cryotherapy in the gastrointestinal tract, especially the esophagus, appears to be well-tolerated and safe. Adverse events are mostly self-limited and include chest pain, esophagitis, sore throat, lip ulcer, esophageal ulcers, and dysphagia. Rates of significant esophageal strictures requiring endoscopic dilation range from 3% to 13%. The significant complication of gastric perforation has been reported with the use of both liquid nitrogen and liquid CO_2 systems. No mortality has been reported with the use of endoscopic cryotherapy [98].

Endoscopic Retrograde Cholangiopancreatography

Biliary Decompression

Whereas ERCP has a decreasing diagnostic role in pancreaticobiliary malignancy (due to the advent of improve CT and MRI, as well as endoscopic ultrasound), it does play a critical role in palliative treatment, especially for patients with unresectable pancreaticobiliary malignancy, through biliary stent placement for obstructive jaundice. However, its role in preoperative drainage for potentially resectable pancreatic malignancy is unclear.

The technical success of biliary stent placement by ERCP for pancreatic malignancy is more than 90%. As the majority of pancreatic cancers present in the head of the pancreas, and the majority of these will present with obstructive jaundice, often resulting in progressive liver dysfunction, pruritus, coagulopathy, and malabsorption, biliary decompression becomes an important treatment goal. As only up to 15% of these patients are potentially surgical resection candidates, the majority will need some form of biliary decompression. Endoscopic biliary decompression has been shown to be less invasive, safer, and more convenient than surgical bypass. Especially for patients with unresectable pancreatic malignancy, it is important in maintaining quality of life and continued medical treatments such as chemotherapy.

Type of Biliary Stents

Initially, plastic biliary stents were used ranging in size from 7 to 11.5 Fr, with the increasing diameter being associated with less stent occlusion. Studies have demonstrated the superiority of biliary stenting with these plastic stents compared with surgical biliary decompression with fewer complications, shorter hospital stays, and lower costs [104–106]. The development of endoscopic biliary self-expandable metal stents offers larger diameter, which is associated with reduced risk of occlusion and longer duration of patency. The original biliary SEMS were uncovered, which were associated with tumor ingrowth (and associated occlusion) and were not easily removed. More recently, partially covered and now fully covered biliary SEMS are associated with less tumor ingrowth and are considered to be more easily removed (if need be). However, there have been concerns about increased rates of cholecystitis (related to cystic duct occlusion), pancreatitis (related to pancreatic duct obstruction), and migration with these covered biliary SEMS.

Multiple studies including a meta-analysis of several RCTs comparing plastic stenting with uncovered SEMS, while showing no significant difference in technical success, therapeutic success rates, or 30-day mortality or complication rate, did show a lower 4-month stent occlusion rate and overall risk of obstruction for uncovered SEMS compared with plastic stents [107]. Although the cost of the SEMS and the ERCP procedure itself influences the analysis, several studies suggest that uncovered SEMS are more cost-effective if the patient's life expectancy is longer than 4–6 months [107, 108].

As tumor ingrowth is a major reason for early occlusion in uncovered SEMS, SEMS covered with a membrane either fully or partially were developed to address this issue. One meta-analysis comprising 1061 patients showed no difference in patency between covered and uncovered SEMS after 6 and 12 months and no difference in rates of pancreatitis, cholecystitis, perforation, bleeding, cholangitis, length of hospital stay, or numbers of recurrent biliary obstruction [109]. However, covered SEMS did have a higher migration rate and a higher rate of tumor overgrowth. Another meta-analysis on 5 fully published RCTs comprising 781 patients showed that while stent dysfunction occurred at a similar rate, there is a trend toward later obstruction with the covered SEMS [110], which also have a significantly longer patency duration and lower frequency of blockage from tumor ingrowth compared with uncovered SEMS. Although there was no difference in the rates of pancreatitis and cholecystitis between covered SEMS and uncovered SEMS in this analysis, the rate of stent migration, tumor ingrowth, and sludge formation was all significantly higher in the covered SEMS groups. Overall, the clinical decision-making about deciding which type of biliary stent to use needs to balance the risks of migration but ability to reintervene if necessary and replace the biliary stents with the likely improved patency rates due to less tumor ingrowth of covered SEMS.

Preoperative Biliary Drainage

For patients with clearly resectable pancreatic malignancy, the role of preoperative biliary drainage remains controversial. Clinical and experimental data had long supported the concept that preoperative hyperbilirubinemia predicted increased postoperative complications, possibly related to affecting nutritional status and immune function. In fact, early studies suggested that there was a link between increased levels of serum bilirubin and an increased incidence of postoperative infectious, renal and nutritional complications, as well as postoperative mortality [111]. More recently, however, several studies—including a randomized controlled trial—suggested that preoperative biliary drainage should be avoided in patients with potentially resectable pancreatic cancer because it is associated with increased morbidity [112]. This multicenter randomized clinical trial compared outcomes of preoperative biliary drainage in a group of patients with clearly resectable disease and those who underwent early surgery and did not have preoperative drainage. The technical success of the preoperative endoscopic biliary drainage was successful in 94%, but with a very high complication rate of 46% including stent occlusion and cholangitis. The overall rate of postsurgical complications were similar, but the rate of serious postoperative complications was significantly higher in the preoperative biliary drainage group [112]. This has then been further supported by a meta-analysis of six RCTs to compare the outcomes of surgery done for biliary obstruction with and without preoperative biliary decompression, which demonstrated significantly higher levels of serious postoperative morbidity in the preoperative biliary drainage group compared with the direct surgery group but without a significant difference in terms of postoperative mortality or length of hospitalization [113]. However, it needs to be remembered that many of these studies did not include patients with marked hyperbilirubinemia. For example, in the RCT by van der Gaag, patients with severe jaundice (total bilirubin >14.6 mg/dL) were excluded from the study [112]. Therefore, the role of preoperative biliary drainage in patients with marked jaundice is unclear. Overall, if the patient is severely jaundiced, or symptomatic with, for example, pruritus, or surgery needs to be delayed to optimize medical comorbidities or to administer neoadjuvant therapy, then preoperative biliary drainage may well be justified.

Role of Biliary Stent Placement in Neoadjuvant Treatment of Pancreatic Cancer

With evolving data supporting neoadjuvant chemotherapy or chemoradiation therapy for potentially resectable patients with pancreatic cancer resulting in improved postsurgical outcomes, and its increasing role in borderline resectable pancreatic cancer, the role for preoperative biliary decompression in this subgroup of patients is becoming better defined [114]. Reliable biliary drainage is required to prevent liver toxicity from some of the chemotherapeutic agents used, which may be required for a period of up to 3 months, before surgery is contemplated. For patients with resectable pancreatic cancer with anticipated surgical resection in less than 3 months, the placement of a plastic biliary stent has often been deemed adequate. The advent of newer neoadjuvant treatment for locally advanced and borderline resectable patients now requires at least 3–4 months of treatment before the patient is reassessed for surgical management. These patients also require increased assurance of prolonged biliary drainage to avoid interruption of medical treatment due to episodes of biliary obstruction or cholangitis. Hence, it does seem reasonable to consider the use of SEMS in this group. However, this is balanced by the issue of cost and the embedding of these stents in the biliary tissue making their removal at surgery more difficult. SEMS have also been associated with the development of a hyperplastic reaction that may interfere with surgical resection, although there is growing evidence that the use of properly placed covered SEMS (due to their ability to prevent tumor ingrowth and hyperplasia and so be removed easily) does not result in increased operative or postoperative complications [115, 116].

Interventional Endoscopic Ultrasound

Endoscopic Ultrasound Celiac Plexus Neurolysis

EUS-guided celiac nerve block is now a well-accepted treatment for the management of pain associated with pancreatic cancer. While similar in technique to either CT or fluoroscopically guided plexus neurolysis, the ability of the EUS linear echoendoscope to accurately identify the celiac plexus and directly guide injection with a local anesthetic (e.g., bupivacaine) and alcohol makes this an easy and safe alternative to standard pain management [117, 118]. A meta-analysis of 119 patients showed the success rate for EUS-guided celiac plexus neurolysis (EUS-CPN) in managing pain in patients with pancreatic cancer of 72% [119]. EUS-guided direct celiac ganglion injection has also been used for the management of pain, but its superiority is unclear [120]. In one small study, positive and complete response rates were significantly higher in the EUS-guided direct celiac ganglia neurolysis group than in the EUS-CPN group [120].

Endoscopic Ultrasound-Fine Needle Injection

EUS-fine needle injection (EUS-FNI) refers to using EUS for direct injection or implantation into the pancreas. The use of EUS-guided fiducial marker implantation to help guide stereotactic body radiation therapy (SBRT) is now currently routinely performed. Fiducial markers are radiopaque seeds that

can be placed with a 19G or 22G needle with technical success rates of 85–100%, and without serious complications. They are implanted in or near the tumor to demarcate its border and facilitate image-guided radiation therapy and so minimize unnecessary radiation to healthy bordering tissue [121–124].

EUS-guided tattooing of the pancreas is also now increasingly used clinically. With improved invasive and noninvasive imaging, even small pancreatic adenocarcinomas and other neoplasms, especially PNETs, are being identified. To assist with perioperative localization, often as these operations are being performed laparoscopically, EUS-guided tattooing using India ink, indocyanine green, and carbon particles is often employed [125–127]. This may be performed several weeks prior to surgical management due to the chronicity of the tattoo.

EUS-guided interventions have also emerged as management and treatment options for patients with pancreatic cancer. A variety of direct injection treatments have been performed experimentally in humans including alcohol, gemcitabine, paclitaxel (OncoGel), oncolytic adenovirus (ONYX-015), immunoreactive agents such as cytoplants, dendritic cells, and TNFerade. Whereas alcohol injection has been most studied for the management of symptomatic nonoperable insulinomas, the most widely studied EUS-FNI treatment for pancreas cancer was TNFerade in a multicenter randomized clinical trial for patients with locally advanced pancreatic cancer [128–130]. While safe with multiple repeat injections, it was not shown to be more effective than standard treatment [128]. EUS-guided ablations with more directed treatments such as radiofrequency ablation and brachytherapy implantation have also been tried in patients with pancreatic cancer. There are at least two clinical studies of the role of EUS implantation of iodine 125 under EUS guidance for unresectable pancreas cancer in combination with chemotherapy. Both studies of EUS-guided brachytherapy showed an improvement in pain symptoms but not overall survival [131, 132].

Endoscopic Ultrasound-Guided Biliary Drainage

Finally, although percutaneous transhepatic biliary drainage or surgical decompression is typically formed for biliary drainage after a failed ERCP, there is increasing data supporting the safety and efficacy of EUS-guided biliary drainage as an alternative, especially in the 3–10% of patients with pancreatic cancer who cannot undergo ERCP biliary decompression, typically due to tumor infiltration in the region of the ampulla. These techniques include EUS-guided rendezvous technique, EUS-guided choledochoduodenostomy, EUS-guided hepaticogastrostomy, and even EUS-guided gallbladder drainage. Typically, either a dilated extrahepatic biliary duct or intrahepatic duct radicle is identified and accessed with a 19-gauge needle under direct EUS guidance. After the tract is dilated, a fully covered metal biliary stent or lumen apposing stent can be deployed for biliary drainage. Technical success rates for this procedure are quoted at over 90%, but it is associated with a 5–10% risk of complications including bile leak and perforation, requiring that this be performed at expert centers [133, 134].

Enteral Stenting

Malignant Esophageal Obstruction

The primary indications for the use of enteral stents in the esophagus are relief of dysphagia and closure of malignant tracheoesophageal fistulae. Esophageal cancers are often unresectable at the time of presentation, and symptomatic palliation of dysphagia with a self-expanding metal stent is central to further management. Alternatives to placing a stent to manage dysphagia include radiation (with or without chemotherapy), laser therapy (thermal or photodynamic), alcohol injection therapy, intermittent dilation, and surgery. However, the treatment options for tracheoesophageal fistula are limited. Stent placement in patients who have tumor involvement within 2 cm of the upper esophageal sphincter is limited by the "foreign body" sensation that develops in these cases. Currently, most stents used in the esophagus are either fully or partially covered. The results of stent placement for palliation of malignant dysphagia and closure of tracheoesophageal fistulae appear to be favorable.

Gastric Outlet Obstruction and Small Intestinal Obstruction

Of patients with pancreatic cancer, 15–20% develop gastric outlet obstruction (GOO) [135–137]. Clinical symptoms of GOO include vomiting, nausea, malnutrition, and dehydration. Most patients with GOO are therefore in a poor clinical condition at presentation and have a short life expectancy if left untreated [138, 139]. Traditionally, open gastrojejunostomy (GJJ) has been the standard palliative treatment in these patients. Laparoscopic GJJ has been introduced as an alternative to open GJJ to relieve symptoms of malignant GOO. Laparoscopic GJJ has been reported to be less invasive and was associated with a faster recovery compared to open GJJ; however, morbidity and mortality of the procedure remained high [137, 139–141].

Enteral stent placement is an attractive alternative treatment [142–145]. It typically involves the placement of a wire across the malignant stricture, followed by a through-the-scope deployment of either a covered or uncovered stent, typically ranging in diameter from 18 to 22 mm and in length from 60 to 120 mm. In the case of pancreatic malignancy, often both biliary stenting and duodenal stenting are required. The technical challenges for this are dependent on the level of the duodenal obstruction. If the level of duodenal obstruction

is proximal to the major papilla, often passage of the duodenoscope through the duodenal stricture is possible (often with dilatation), in order to perform biliary stenting prior to placement of the duodenal stent. Other approaches in this setting include placement of a duodenal stent followed either immediately or after a few days by advancement of the duodenoscope through the duodenal stent for placement of the biliary stent. Alternatively, EUS-guided biliary drainage or a percutaneous biliary decompression may be necessary. When the obstruction in the 2nd duodenum also involves the major papilla, it can be very difficult to place a biliary stent by ERCP. Under these circumstances, a duodenal stent is placed followed by either EUS-guided biliary drainage via a hepaticojejunostomy or choledochoduodenostomy or percutaneous biliary drainage. For the scenario of duodenal obstruction distal to the papilla, the sequence of placement of both the duodenal and biliary stents is not critical.

Several studies have demonstrated that SEMS placement is associated with faster resumption of oral intake, shorter postprocedural hospital stays, lesser morbidity, and lower costs compared with gastrojejunostomy [127, 146–148]. In a systemic review, we compared the outcome of GJJ with that of duodenal stent placement [149]. A total of 44 studies were selected including only 2 randomized trials (with 27 and 18 patients) [150, 151]. A total of 1046 patients received a duodenal stent, which, in most cases, was an uncovered enteral metal stent, with a stent diameter of 20–24 mm, whereas 297 patients underwent GJJ. This review showed that initial clinical success was higher after stent placement (89% vs. 72%). Major complication rates were, however, similar (early: 7% vs. 6%, respectively; and late: 18% vs. 17%, respectively). Recurrent obstructive symptoms were more commonly seen after stent placement, whereas hospital stay was shorter after stent placement. The results of this review suggested that stent placement is associated with more favorable results in patients with a relatively short life expectancy, while GJJ is preferable in patients with a better prognosis [149]. More recently EUS-guided gastrojejunostomy has been reported as a novel alternative to enteral stent placement for management of malignant gastric outlet obstruction.

Colonic Obstruction

Left-sided colonic obstruction may be an emergency caused by primary or recurrent colorectal carcinoma in up to 33% of patients with these cancers [152]. In primary colorectal cancer, initial surgical management typically involves emergent colostomy with or without tumor resection. A second operation is therefore required for resection, and a third is performed at a later date for takedown of the colostomy. In poor surgical candidates or patients with recurrent disease, palliative colostomy is performed. Postoperative mortality rates have improved during the past decade but are still estimated to be 7%. Expandable metal stents are placed as an alternative to surgical colostomy for two clinical indications: (1) preoperative relief of malignant colonic obstruction, which allows colonic decompression and cleansing before elective one-stage tumor resection and primary anastomosis and (2) palliative treatment of malignant colonic obstruction.

The technical success rate for placement of self-expanding metal stents for malignant colonic obstruction approaches 100%; however, in 6% of cases, immediate decompression is not achieved. Causes of early stent failure include poor expansion, incomplete stenting of the stricture, fecal impaction, stent migration, and the presence of an unrecognized additional proximal malignant stricture. Late causes of obstruction following colonic stent placement are usually tumor ingrowth or overgrowth. Stent patency may be reestablished with laser ablation, photodynamic therapy, or the insertion of an additional stent [152].

Cost-benefit analyses have shown that stenting with subsequent elective surgery is less expensive than emergency surgery for treating complete colorectal obstruction, and the median time in the hospital is decreased when a stent is used as a bridge to surgery [152]. However, the debate persists over the role of self-expandable metallic stent (SEMS) placement as a bridge to elective surgery for symptomatic left-sided malignant colonic obstruction. Originally, decision analysis was used to compare the cost-effectiveness of the two competing strategies. Colonic stent resulted in 23% fewer operative procedures per patient, an 83% reduction in stoma requirement (7% vs. 43%), and lower procedure-related mortality (5% vs. 11%). This study concluded that colonic stent insertion followed by elective surgery appears more effective and less costly than emergency surgery under base-case conditions [152]. A more recent meta-analysis and systematic review on the subject showed that colon stenting was associated with lower short-term overall morbidity and lower rates of temporary and permanent stoma. Depending on multiple factors such as local expertise, clinical status including level of obstruction, and level of certainty of diagnosis, colonic stenting does offer some advantages with less risk than emergency surgery for left-sided malignant colonic obstruction in the short term [153].

Natural Orifice Transluminal Endoscopic Surgery Technique

NOTES is a minimally invasive surgery that can be performed with an endoscope passed through a natural orifice (e.g., mouth, anus) and then through an internal incision in the stomach, vagina, bladder, or colon [154]. It typically avoids the need for skin incision and has the potential main advantages of faster recovery with shorter hospital stays, lower anesthesia requirements, avoidance of the potential complications of transabdominal wound infections, and better

postoperative pulmonary and diaphragmatic function. Clinically, NOTES has ranged from diagnostic explorations of the peritoneal cavity to complex organ resections including pancreatectomy, splenectomy, cholecystectomy, gastrojejunostomy, and nephrectomy [155]. However, overall NOTES safety and efficacy is unclear compared with effective minimally invasive surgical options such as laparoscopic surgery [156].

References

1. Hirschowitz BI, Curtiss LE, Peters CW, Pollard HM. Demonstration of a new gastroscope, the fiberscope. Gastroenterology. 1958;35(1):50; discussion 51–53.
2. Kiesslich R, Burg J, Vieth M, Gnaendiger J, Enders M, Delaney P, et al. Confocal laser endoscopy for diagnosing intraepithelial neoplasias and colorectal cancer in vivo. Gastroenterology. 2004;127(3):706–13.
3. Neumann H, Kiesslich R, Wallace MB, Neurath MF. Confocal laser endomicroscopy: technical advances and clinical applications. Gastroenterology. 2010;139(2):388–92, 392. e381–382.
4. Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology. 2007;132(3):874–82.
5. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology. 1997;112(4):1087–95.
6. Savides TJ. Tricks for improving EUS-FNA accuracy and maximizing cellular yield. Gastrointest Endosc. 2009;69(2 Suppl):S130–3.
7. Varadarajulu S, Bang JY, Hebert-Magee S. Assessment of the technical performance of the flexible 19-gauge EUS-FNA needle. Gastrointest Endosc. 2012;76(2):336–43.
8. Lee JG, Leung J. Tissue sampling at ERCP in suspected pancreatic cancer. Gastrointest Endosc Clin N Am. 1998;8(1):221–35.
9. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75(2):319–31.
10. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass? a meta-analysis and systematic review. Pancreas. 2013;42(1):20–6.
11. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol. 2002;97(6):1386–91.
12. Horwhat JD, Paulson EK, McGrath K, Branch MS, Baillie J, Tyler D, et al. A randomized comparison of EUS-guided FNA versus CT or US-guided FNA for the evaluation of pancreatic mass lesions. Gastrointest Endosc. 2006;63(7):966–75.
13. Volmar KE, Vollmer RT, Jowell PS, Nelson RC, Xie HB. Pancreatic FNA in 1000 cases: a comparison of imaging modalities. Gastrointest Endosc. 2005;61(7):854–61.
14. Wang W, Shpaner A, Krishna SG, Ross WA, Bhutani MS, Tamm EP, et al. Use of EUS-FNA in diagnosing pancreatic neoplasm without a definitive mass on CT. Gastrointest Endosc. 2013;78(1):73–80.
15. Micames C, Jowell PS, White R, Paulson E, Nelson R, Morse M, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc. 2003;58(5):690–5.
16. Eloubeidi MA, Gress FG, Savides TJ, Wiersema MJ, Kochman ML, Ahmad NA, et al. Acute pancreatitis after EUS-guided FNA of solid pancreatic masses: a pooled analysis from EUS centers in the United States. Gastrointest Endosc. 2004;60(3):385–9.
17. Eloubeidi MA, Tamhane A, Varadarajulu S, Wilcox CM. Frequency of major complications after EUS-guided FNA of solid pancreatic masses: a prospective evaluation. Gastrointest Endosc. 2006;63(4):622–9.
18. Tierney WM, Fendrick AM, Hirth RA, Scheiman JM. The clinical and economic impact of alternative staging strategies for adenocarcinoma of the pancreas. Am J Gastroenterol. 2000;95(7):1708–13.
19. Harewood GC, Wiersema MJ. A cost analysis of endoscopic ultrasound in the evaluation of pancreatic head adenocarcinoma. Am J Gastroenterol. 2001;96(9):2651–6.
20. Mertz H, Gautam S. The learning curve for EUS-guided FNA of pancreatic cancer. Gastrointest Endosc. 2004;59(1):33–7.
21. Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. Am J Gastroenterol. 2003;98(6):1289–94.
22. Farrell JJ. Diagnosing pancreatic malignancy in the setting of chronic pancreatitis: is there room for improvement? Gastrointest Endosc. 2005;62(5):737–41.
23. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc. 2005;62(5):728–36; quiz 751, 753.
24. Fritscher-Ravens A, Brand L, Knofel WT, Bobrowski C, Topalidis T, Thonke F, et al. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. Am J Gastroenterol. 2002;97(11):2768–75.
25. Atiq M, Bhutani MS, Ross WA, Raju GS, Gong Y, Tamm EP, et al. Role of endoscopic ultrasonography in evaluation of metastatic lesions to the pancreas: a tertiary cancer center experience. Pancreas. 2013;42(3):516–23.
26. Tharian B, Tsiopoulos F, George N, Pietro SD, Attili F, Larghi A. Endoscopic ultrasound fine needle aspiration: technique and applications in clinical practice. World J Gastrointest Endosc. 2012;4(12):532–44.
27. Varadarajulu S, Fockens P, Hawes RH. Best practices in endoscopic ultrasound-guided fine-needle aspiration. Clin Gastroenterol Hepatol. 2012;10(7):697–703.
28. Weston BR, Bhutani MS. Optimizing diagnostic yield for EUS-guided sampling of solid pancreatic lesions: a technical review. Gastroenterol Hepatol. 2013;9(6):352–63.
29. Polkowski M, Larghi A, Weynand B, Boustiere C, Giovannini M, Pujol B, et al. Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) technical guideline. Endoscopy. 2012;44(2):190–206.
30. Varadarajulu S, Hasan MK, Bang JY, Hebert-Magee S, Hawes RH. Endoscopic ultrasound-guided tissue acquisition. Dig Endosc. 2014;26(Suppl 1):62–9.
31. Panic N, Larghi A. Techniques for endoscopic ultrasound-guided fine-needle biopsy. Gastrointest Endosc Clin N Am. 2014;24(1):83–107.
32. Donahue TR, Nguyen AH, Moughan J, Li L, Tatishchev S, Toste P, et al. Stromal microrna-21 levels predict response to 5-fluorouracil in patients with pancreatic cancer. J Surg Oncol. 2014;110(8):952–9.
33. Neuzillet C, Tijeras-Raballand A, Cros J, Faivre S, Hammel P, Raymond E. Stromal expression of SPARC in pancreatic adenocarcinoma. Cancer Metastasis Rev. 2013;32(3–4):585–602.

34. Simone NL, Paweletz CP, Charboneau L, Petricoin EF 3rd, Liotta LA. Laser capture microdissection: beyond functional genomics to proteomics. Mol Diagn. 2000;5(4):301–7.
35. Saftoiu A, Vilmann P, Gorunescu F, Gheonea DI, Gorunescu M, Ciurea T, et al. Neural network analysis of dynamic sequences of EUS elastography used for the differential diagnosis of chronic pancreatitis and pancreatic cancer. Gastrointest Endosc. 2008;68(6):1086–94.
36. Fuccio L, Hassan C, Laterza L, Correale L, Pagano N, Bocus P, et al. The role of k-ras gene mutation analysis in EUS-guided FNA cytology specimens for the differential diagnosis of pancreatic solid masses: a meta-analysis of prospective studies. Gastrointest Endosc. 2013;78(4):596–608.
37. Parsi MA, Jang S, Sanaka M, Stevens T, Vargo JJ. Diagnostic and therapeutic cholangiopancreatoscopy: performance of a new digital cholangioscope. Gastrointest Endosc. 2014;79(6):936–42.
38. de la Serna-Higuera C, Perez-Miranda M, Diez-Redondo P, Gil-Simon P, Herranz T, Perez-Martin E, et al. EUS-guided single-incision needle-knife biopsy: description and results of a new method for tissue sampling of subepithelial GI tumors (with video). Gastrointest Endosc. 2011;74(3):672–6.
39. Nishizawa T, Yahagi N. Endoscopic mucosal resection and endoscopic submucosal dissection: technique and new directions. Curr Opin Gastroenterol. 2017;33:315–9.
40. Fujishiro M, Yahagi N, Kashimura K, Mizushima Y, Oka M, Matsuura T, et al. Different mixtures of sodium hyaluronate and their ability to create submucosal fluid cushions for endoscopic mucosal resection. Endoscopy. 2004;36(7):584–9.
41. Conio M, Rajan E, Sorbi D, Norton I, Herman L, Filiberti R, et al. Comparative performance in the porcine esophagus of different solutions used for submucosal injection. Gastrointest Endosc. 2002;56(4):513–6.
42. Fujishiro M, Yahagi N, Kashimura K, Mizushima Y, Oka M, Enomoto S, et al. Comparison of various submucosal injection solutions for maintaining mucosal elevation during endoscopic mucosal resection. Endoscopy. 2004;36(7):579–83.
43. Fleischer DE, Wang GQ, Dawsey S, Tio TL, Newsome J, Kidwell J, et al. Tissue band ligation followed by snare resection (band and snare): a new technique for tissue acquisition in the esophagus. Gastrointest Endosc. 1996;44(1):68–72.
44. Inoue H, Kawano T, Tani M, Takeshita K, Iwai T. Endoscopic mucosal resection using a cap: techniques for use and preventing perforation. Can J Gastroenterol. 1999;13(6):477–80.
45. Rajan E, Gostout CJ, Feitoza AB, Leontovich ON, Herman LJ, Burgart LJ, et al. Widespread EMR: a new technique for removal of large areas of mucosa. Gastrointest Endosc. 2004;60(4):623–7.
46. Ono H. Endoscopic submucosal dissection for early gastric cancer. Chin J Dig Dis. 2005;6(3):119–21.
47. Hayashi N, Tanaka S, Nishiyama S, Terasaki M, Nakadoi K, Oka S, et al. Predictors of incomplete resection and perforation associated with endoscopic submucosal dissection for colorectal tumors. Gastrointest Endosc. 2014;79(3):427–35.
48. Toyonaga T, Man IM, Morita Y, Azuma T. Endoscopic submucosal dissection (ESD) versus simplified/hybrid ESD. Gastrointest Endosc Clin N Am. 2014;24(2):191–9.
49. Tomizawa Y, Iyer PG, Wong Kee Song LM, Buttar NS, Lutzke LS, Wang KK. Safety of endoscopic mucosal resection for Barrett's esophagus. Am J Gastroenterol. 2013;108(9):1440–7; quiz 1448.
50. Katada C, Muto M, Manabe T, Boku N, Ohtsu A, Yoshida S. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. Gastrointest Endosc. 2003;57(2):165–9.
51. Ahmad NA, Kochman ML, Long WB, Furth EE, Ginsberg GG. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. Gastrointest Endosc. 2002;55(3):390–6.
52. Koh R, Hirasawa K, Yahara S, Oka H, Sugimori K, Morimoto M, et al. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. Gastrointest Endosc. 2013;78(3):476–83.
53. Park YM, Cho E, Kang HY, Kim JM. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. Surg Endosc. 2011;25(8):2666–77.
54. Binmoeller KF, Grimm H, Soehendra N. Endoscopic closure of a perforation using metallic clips after snare excision of a gastric leiomyoma. Gastrointest Endosc. 1993;39(2):172–4.
55. Jung D, Youn YH, Jahng J, Kim JH, Park H. Risk of electrocoagulation syndrome after endoscopic submucosal dissection in the colon and rectum. Endoscopy. 2013;45(9):714–7.
56. Soehendra N, Binmoeller KF, Bohnacker S, Seitz U, Brand B, Thonke F, et al. Endoscopic snare mucosectomy in the esophagus without any additional equipment: a simple technique for resection of flat early cancer. Endoscopy. 1997;29(5):380–3.
57. Pacifico RJ, Wang KK, Wongkeesong LM, Buttar NS, Lutzke LS. Combined endoscopic mucosal resection and photodynamic therapy versus esophagectomy for management of early adenocarcinoma in Barrett's esophagus. Clin Gastroenterol Hepatol. 2003;1(4):252–7.
58. Pech O, Gossner L, May A, Vieth M, Stolte M, Ell C. Endoscopic resection of superficial esophageal squamous-cell carcinomas: western experience. Am J Gastroenterol. 2004;99(7):1226–32.
59. Seewald S, Akaraviputh T, Seitz U, Brand B, Groth S, Mendoza G, et al. Circumferential EMR and complete removal of Barrett's epithelium: a new approach to management of Barrett's esophagus containing high-grade intraepithelial neoplasia and intramucosal carcinoma. Gastrointest Endosc. 2003;57(7):854–9.
60. Merkow RP, Bilimoria KY, Keswani RN, Chung J, Sherman KL, Knab LM, et al. Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer. J Natl Cancer Inst. 2014;106(7):dju133.
61. Pech O, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut. 2008;57(9):1200–6.
62. Saligram S, Chennat J, Hu H, Davison JM, Fasanella KE, McGrath K. Endotherapy for superficial adenocarcinoma of the esophagus: an American experience. Gastrointest Endosc. 2013;77(6):872–6.
63. Nakagawa K, Koike T, Iijima K, Shinkai H, Hatta W, Endo H, et al. Comparison of the long-term outcomes of endoscopic resection for superficial squamous cell carcinoma and adenocarcinoma of the esophagus in Japan. Am J Gastroenterol. 2014;109(3):348–56.
64. Nomura T, Boku N, Ohtsu A, Muto M, Matsumoto S, Tajiri H, et al. Recurrence after endoscopic mucosal resection for superficial esophageal cancer. Endoscopy. 2000;32(4):277–80.
65. Gotoda T. Endoscopic resection of early gastric cancer: the Japanese perspective. Curr Opin Gastroenterol. 2006;22(5):561–9.
66. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol. 2005;23(20):4490–8.
67. Min BH, Kang KJ, Lee JH, Kim ER, Min YW, Rhee PL, et al. Endoscopic resection for undifferentiated early gastric cancer: focusing on histologic discrepancies between forceps biopsy-based and endoscopic resection specimen-based diagnosis. Dig Dis Sci. 2014;59(10):2536–43.
68. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer. 2000;3(4):219–25.
69. Kojima T, Parra-Blanco A, Takahashi H, Fujita R. Outcome of endoscopic mucosal resection for early gastric cancer: review of

the Japanese literature. Gastrointest Endosc. 1998;48(5):550–4; discussion 554–555.
70. Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T, et al. Differences in diagnostic criteria for gastric carcinoma between Japanese and western pathologists. Lancet. 1997;349(9067):1725–9.
71. Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, et al. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. Gastrointest Endosc. 2006;64(6):877–83.
72. Takekoshi T, Baba Y, Ota H, Kato Y, Yanagisawa A, Takagi K, et al. Endoscopic resection of early gastric carcinoma: results of a retrospective analysis of 308 cases. Endoscopy. 1994;26(4):352–8.
73. Hiki Y, Shimao H, Mieno H, Sakakibara Y, Kobayashi N, Saigenji K. Modified treatment of early gastric cancer: evaluation of endoscopic treatment of early gastric cancers with respect to treatment indication groups. World J Surg. 1995;19(4):517–22.
74. Choi KS, Jung HY, Choi KD, Lee GH, Song HJ, Kim DH, et al. EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes. Gastrointest Endosc. 2011;73(5):942–8.
75. Etoh T, Katai H, Fukagawa T, Sano T, Oda I, Gotoda T, et al. Treatment of early gastric cancer in the elderly patient: results of EMR and gastrectomy at a national referral center in Japan. Gastrointest Endosc. 2005;62(6):868–71.
76. Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. Endoscopy. 2014;46(5):388–402.
77. Yokota T, Sugihara K, Yoshida S. Endoscopic mucosal resection for colorectal neoplastic lesions. Dis Colon Rectum. 1994;37(11):1108–11.
78. Puli SR, Kakugawa Y, Saito Y, Antillon D, Gotoda T, Antillon MR. Successful complete cure en-bloc resection of large nonpedunculated colonic polyps by endoscopic submucosal dissection: a meta-analysis and systematic review. Ann Surg Oncol. 2009;16(8):2147–51.
79. Ikematsu H, Yoda Y, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology. 2013;144(3):551–9; quiz e514.
80. Yoda Y, Ikematsu H, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, et al. A large-scale multicenter study of long-term outcomes after endoscopic resection for submucosal invasive colorectal cancer. Endoscopy. 2013;45(9):718–24.
81. He L, Deng T, Luo H. Efficacy and safety of endoscopic resection therapies for rectal carcinoid tumors: a meta-analysis. Yonsei Med J. 2015;56(1):72–81.
82. Bialek A, Wiechowska-Kozlowska A, Pertkiewicz J, Polkowski M, Milkiewicz P, Karpinska K, et al. Endoscopic submucosal dissection for treatment of gastric subepithelial tumors (with video). Gastrointest Endosc. 2012;75(2):276–86.
83. Joo MK, Park JJ, Kim H, Koh JS, Lee BJ, Chun HJ, et al. Endoscopic versus surgical resection of GI stromal tumors in the upper GI tract. Gastrointest Endosc. 2016;83(2):318–26.
84. Chen H, Xu Z, Huo J, Liu D. Submucosal tunneling endoscopic resection for simultaneous esophageal and cardia submucosal tumors originating from the muscularis propria layer (with video). Dig Endosc. 2015;27(1):155–8.
85. Chen T, Zhang C, Yao LQ, Zhou PH, Zhong YS, Zhang YQ, et al. Management of the complications of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors. Endoscopy. 2016;48(2):149–55.
86. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009;360(22):2277–88.
87. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(10):1245–55.
88. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. Am J Gastroenterol. 2011;106(11):1899–908; quiz 1909.
89. Phoa KN, Pouw RE, Bisschops R, Pech O, Ragunath K, Weusten BL, et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European Multicentre Study (EURO-II). Gut. 2016;65(4):555–62.
90. Phoa KN, van Vilsteren FG, Weusten BL, Bisschops R, Schoon EJ, Ragunath K, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014;311(12):1209–17.
91. Wolf WA, Pasricha S, Cotton C, Li N, Triadafilopoulos G, Muthusamy VR, et al. Incidence of esophageal adenocarcinoma and causes of mortality after radiofrequency ablation of Barrett's esophagus. Gastroenterology. 2015;149(7):1752–61. e1751.
92. Haidry RJ, Butt MA, Dunn J, Banks M, Gupta A, Smart H, et al. Radiofrequency ablation for early oesophageal squamous neoplasia: outcomes form United Kingdom registry. World J Gastroenterol. 2013;19(36):6011–9.
93. Smith I, Kahaleh M. Biliary tumor ablation with photodynamic therapy and radiofrequency ablation. Gastrointest Endosc Clin N Am. 2015;25(4):793–804.
94. Ortner ME, Caca K, Berr F, Liebetruth J, Mansmann U, Huster D, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology. 2003;125(5):1355–63.
95. Strand DS, Cosgrove ND, Patrie JT, Cox DG, Bauer TW, Adams RB, et al. ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. Gastrointest Endosc. 2014;80(5):794–804.
96. Signoretti M, Valente R, Repici A, Delle Fave G, Capurso G, Carrara S. Endoscopy-guided ablation of pancreatic lesions: technical possibilities and clinical outlook. World J Gastrointest Endosc. 2017;9(2):41–54.
97. Pai M, Habib N, Senturk H, Lakhtakia S, Reddy N, Cicinnati VR, et al. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg. 2015;7(4):52–9.
98. Parsi M, Trindale A, Bhutani M. Cryotherapy in gastrointestinal endoscopy. VideoGIE. 2017;2(5):89–95.
99. Ghorbani S, Tsai FC, Greenwald BD, Jang S, Dumot JA, McKinley MJ, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's dysplasia: results of the national cryospray registry. Dis Esophagus. 2016;29(3):241–7.
100. Gosain S, Mercer K, Twaddell WS, Uradomo L, Greenwald BD. Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: long-term results. Gastrointest Endosc. 2013;78(2):260–5.
101. Halsey KD, Chang JW, Waldt A, Greenwald BD. Recurrent disease following endoscopic ablation of Barrett's high-grade dysplasia with spray cryotherapy. Endoscopy. 2011;43(10):844–8.
102. Sengupta N, Ketwaroo GA, Bak DM, Kedar V, Chuttani R, Berzin TM, et al. Salvage cryotherapy after failed radiofrequency ablation for Barrett's esophagus-related dysplasia is safe and effective. Gastrointest Endosc. 2015;82(3):443–8.
103. Greenwald BD, Dumot JA, Abrams JA, Lightdale CJ, David DS, Nishioka NS, et al. Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. Gastrointest Endosc. 2010;71(4):686–93.
104. Murakami M, Shimizu J, Kim Y, Kim HM, Souma Y, Hirota M, et al. Bypass surgery or stent placement for biliary obstruction

in patients with unresectable pancreatic cancer. Gan To Kagaku Ryoho. 2013;40(12):1705–7.
105. Yamamoto R, Takahashi M, Osafune Y, Chinen K, Kato S, Nagoshi S, et al. Comparison of endoscopic stenting for malignant biliary obstruction: a single-center study. World J Gastrointest Endosc. 2015;7(9):889–94.
106. Kofokotsios A, Papazisis K, Andronikidis I, Ntinas A, Kardassis D, Vrochides D. Palliation with endoscopic metal stents may be preferable to surgical intervention for patients with obstructive pancreatic head adenocarcinoma. Int Surg. 2015;100(6):1104–10.
107. Moss AC, Morris E, Leyden J, MacMathuna P. Do the benefits of metal stents justify the costs? A systematic review and meta-analysis of trials comparing endoscopic stents for malignant biliary obstruction. Eur J Gastroenterol Hepatol. 2007;19(12):1119–24.
108. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev. 2006;(1):CD004200.
109. Almadi MA, Barkun AN, Martel M. No benefit of covered vs uncovered self-expandable metal stents in patients with malignant distal biliary obstruction: a meta-analysis. Clin Gastroenterol Hepatol. 2013;11(1):27–37.e21.
110. Saleem A, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. Gastrointest Endosc. 2011;74(2):321–7. e321–323.
111. Cote GA, Sherman S. Endoscopic palliation of pancreatic cancer. Cancer J. 2012;18(6):584–90.
112. van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362(2):129–37.
113. Fang Y, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, et al. Pre-operative biliary drainage for obstructive jaundice. Cochrane Database Syst Rev. 2012;(9):CD005444.
114. Abrams RA, Lowy AM, O'Reilly EM, Wolff RA, Picozzi VJ, Pisters PW. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1751–6.
115. Mullen JT, Lee JH, Gomez HF, Ross WA, Fukami N, Wolff RA, et al. Pancreaticoduodenectomy after placement of endobiliary metal stents. J Gastrointest Surg. 2005;9(8):1094–104; discussion 1104–1095.
116. Wasan SM, Ross WA, Staerkel GA, Lee JH. Use of expandable metallic biliary stents in resectable pancreatic cancer. Am J Gastroenterol. 2005;100(9):2056–61.
117. Luz LP, Al-Haddad MA, DeWitt JA. EUS-guided celiac plexus interventions in pancreatic cancer pain: an update and controversies for the endosonographer. Endosc Ultrasound. 2014;3(4):213–20.
118. Fujii-Lau LL, Bamlet WR, Eldrige JS, Chari ST, Gleeson FC, Abu Dayyeh BK, et al. Impact of celiac neurolysis on survival in patients with pancreatic cancer. Gastrointest Endosc. 2015;82(1):46–56.e42.
119. Kaufman M, Singh G, Das S, Concha-Parra R, Erber J, Micames C, et al. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. J Clin Gastroenterol. 2010;44(2):127–34.
120. Doi S, Yasuda I, Kawakami H, Hayashi T, Hisai H, Irisawa A, et al. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. Endoscopy. 2013;45(5):362–9.
121. DiMaio CJ, Nagula S, Goodman KA, Ho AY, Markowitz AJ, Schattner MA, et al. EUS-guided fiducial placement for image-guided radiation therapy in GI malignancies by using a 22-gauge needle (with videos). Gastrointest Endosc. 2010;71(7):1204–10.
122. Pishvaian AC, Collins B, Gagnon G, Ahlawat S, Haddad NG. EUS-guided fiducial placement for cyberknife radiotherapy of mediastinal and abdominal malignancies. Gastrointest Endosc. 2006;64(3):412–7.
123. Park WG, Yan BM, Schellenberg D, Kim J, Chang DT, Koong A, et al. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. Gastrointest Endosc. 2010;71(3):513–8.
124. Varadarajulu S, Trevino JM, Shen S, Jacob R. The use of endoscopic ultrasound-guided gold markers in image-guided radiation therapy of pancreatic cancers: a case series. Endoscopy. 2010;42(5):423–5.
125. Farrell JJ, Sherrod A, Parekh D. EUS-guided fine-needle tattooing for preoperative localization of early pancreatic adenocarcinoma. Gastrointest Endosc. 2009;69(1):176–7.
126. Lennon AM, Newman N, Makary MA, Edil BH, Shin EJ, Khashab MA, et al. EUS-guided tattooing before laparoscopic distal pancreatic resection (with video). Gastrointest Endosc. 2010;72(5):1089–94.
127. Larsen MH, Fristrup CW, Mortensen MB. Endoscopic ultrasound-guided fine-needle marking of a small pancreatic tumor. Endoscopy. 2009;41(Suppl 2):E175–6.
128. Hecht JR, Farrell JJ, Senzer N, Nemunaitis J, Rosemurgy A, Chung T, et al. EUS or percutaneously guided intratumoral tnferade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. Gastrointest Endosc. 2012;75(2):332–8.
129. Jurgensen C, Schuppan D, Neser F, Ernstberger J, Junghans U, Stolzel U. EUS-guided alcohol ablation of an insulinoma. Gastrointest Endosc. 2006;63(7):1059–62.
130. Levy MJ, Thompson GB, Topazian MD, Callstrom MR, Grant CS, Vella A. US-guided ethanol ablation of insulinomas: a new treatment option. Gastrointest Endosc. 2012;75(1):200–6.
131. Du YQ, Li ZS, Jin ZD. Endoscope-assisted brachytherapy for pancreatic cancer: from tumor killing to pain relief and drainage. J Interv Gastroenterol. 2011;1(1):23–7.
132. Jin Z, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. Endoscopy. 2008;40(4):314–20.
133. Poincloux L, Rouquette O, Buc E, Privat J, Pezet D, Dapoigny M, et al. Endoscopic ultrasound-guided biliary drainage after failed ERCP: cumulative experience of 101 procedures at a single center. Endoscopy. 2015;47(9):794–801.
134. Weilert F. Prospective evaluation of simplified algorithm for EUS-guided intra-hepatic biliary access and anterograde interventions for failed ERCP. Surg Endosc. 2014;28(11):3193–9.
135. Adler DG, Baron TH. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: experience in 36 patients. Am J Gastroenterol. 2002;97(1):72–8.
136. Espinel J, Vivas S, Munoz F, Jorquera F, Olcoz JL. Palliative treatment of malignant obstruction of gastric outlet using an endoscopically placed enteral wallstent. Dig Dis Sci. 2001;46(11):2322–4.
137. Lopera JE, Brazzini A, Gonzales A, Castaneda-Zuniga WR. Gastroduodenal stent placement: current status. Radiographics. 2004;24(6):1561–73.
138. Del Piano M, Ballare M, Montino F, Todesco A, Orsello M, Magnani C, et al. Endoscopy or surgery for malignant GI outlet obstruction? Gastrointest Endosc. 2005;61(3):421–6.
139. Wong YT, Brams DM, Munson L, Sanders L, Heiss F, Chase M, et al. Gastric outlet obstruction secondary to pancreatic cancer: surgical vs endoscopic palliation. Surg Endosc. 2002;16(2):310–2.
140. Bessoud B, de Baere T, Denys A, Kuoch V, Ducreux M, Precetti S, et al. Malignant gastroduodenal obstruction: palliation with

self-expanding metallic stents. J Vasc Interv Radiol. 2005;16(2 Pt 1):247–53.
141. Brune IB, Feussner H, Neuhaus H, Classen M, Siewert JR. Laparoscopic gastrojejunostomy and endoscopic biliary stent placement for palliation of incurable gastric outlet obstruction with cholestasis. Surg Endosc. 1997;11(8):834–7.
142. Holt AP, Patel M, Ahmed MM. Palliation of patients with malignant gastroduodenal obstruction with self-expanding metallic stents: the treatment of choice? Gastrointest Endosc. 2004;60(6):1010–7.
143. Kim JH, Yoo BM, Lee KJ, Hahm KB, Cho SW, Park JJ, et al. Self-expanding coil stent with a long delivery system for palliation of unresectable malignant gastric outlet obstruction: a prospective study. Endoscopy. 2001;33(10):838–42.
144. Telford JJ, Carr-Locke DL, Baron TH, Tringali A, Parsons WG, Gabbrielli A, et al. Palliation of patients with malignant gastric outlet obstruction with the enteral wallstent: outcomes from a multicenter study. Gastrointest Endosc. 2004;60(6):916–20.
145. Song HY, Shin JH, Yoon CJ, Lee GH, Kim TW, Lee SK, et al. A dual expandable nitinol stent: experience in 102 patients with malignant gastroduodenal strictures. J Vasc Interv Radiol. 2004;15(12):1443–9.
146. Jeurnink SM, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc. 2010;71(3):490–9.
147. Tringali A, Didden P, Repici A, Spaander M, Bourke MJ, Williams SJ, et al. Endoscopic treatment of malignant gastric and duodenal strictures: a prospective, multicenter study. Gastrointest Endosc. 2014;79(1):66–75.
148. Hosono S, Ohtani H, Arimoto Y, Kanamiya Y. Endoscopic stenting versus surgical gastroenterostomy for palliation of malignant gastroduodenal obstruction: a meta-analysis. J Gastroenterol. 2007;42(4):283–90.
149. Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol. 2007;7:1–10.
150. Fiori E, Lamazza A, Volpino P, Burza A, Paparelli C, Cavallaro G, et al. Palliative management of malignant antro-pyloric strictures. Gastroenterostomy vs. endoscopic stenting. A randomized prospective trial. Anticancer Res. 2004;24(1):269–71.
151. Mehta S, Hindmarsh A, Cheong E, Cockburn J, Saada J, Tighe R, et al. Prospective randomized trial of laparoscopic gastrojejunostomy versus duodenal stenting for malignant gastric outflow obstruction. Surg Endosc. 2006;20(2):239–42.
152. Targownik LE, Spiegel BM, Sack J, Hines OJ, Dulai GS, Gralnek IM, et al. Colonic stent vs. emergency surgery for management of acute left-sided malignant colonic obstruction: a decision analysis. Gastrointest Endosc. 2004;60(6):865–74.
153. Cennamo V, Luigiano C, Coccolini F, Fabbri C, Bassi M, De Caro G, et al. Meta-analysis of randomized trials comparing endoscopic stenting and surgical decompression for colorectal cancer obstruction. Int J Color Dis. 2013;28(6):855–63.
154. Ko CW, Kalloo AN. Per-oral transgastric abdominal surgery. Chin J Dig Dis. 2006;7(2):67–70.
155. Swanstrom LL, Kozarek R, Pasricha PJ, Gross S, Birkett D, Park PO, et al. Development of a new access device for transgastric surgery. J Gastrointest Surg. 2005;9(8):1129–36; discussion 1136–1127.
156. Bernhardt J, Sasse S, Ludwig K, Meier PN. Update in natural orifice translumenal endoscopic surgery (notes). Curr Opin Gastroenterol. 2017;33:346–51.
157. Samdani TS, Sonoda T. Endoscopic mucosal resection: colon and rectum. In: Kroh M, Reavis K, editors. The SAGES manual operating through the endoscope. Cham: Springer; 2016.
158. Hammad H, Kaltenbach T, Soetikno R. Endoscopic submucosal dissection for malignant esophageal lesions. Curr Gastroenterol Rep. 2014;16:386.

Role of Interventional Radiology in Management of Gastrointestinal Cancers and Neuroendocrine Tumors

31

Ali Devrim Karaosmanoglu, Mehmet Ruhi Onur, and Okan Akhan

Introduction

Interventional radiology (IR) has come a long way since the days of Charles Dotter, who performed the first angioplasty by using a combination of basic guidewires and catheters for dilating the focal stenosis in the superficial femoral artery in a patient with leg ischemia and gangrene [1]. In the last three decades, IR has made unparalleled progress owing to the vigorous clinical and research efforts of interventional radiologists on top of contributions from the industry in terms of development of state-of-art medical equipment widely used in IR practice.

Interventional oncology (IO) refers to interventional radiologists performing procedures for diagnosing and treating patients who are already suspected of having cancer. Interventional radiologists have made great advances, and today they account for irreplaceable members of multidisciplinary cancer management teams in tertiary-care centers.

In this chapter, we aim to provide the readers with an updated overview of IR applications in clinical oncology.

Image-Guided Biopsy for Diagnosis

The diagnosis of gastrointestinal cancer typically starts with imaging followed by histopathologic examination, with the exception of patients endoscopically diagnosed with luminal cancers such as gastroesophageal or colorectal cancers. Accurate diagnosis typically relies on obtaining an adequate specimen representing the suspected tumor mass. With the advance in biopsy devices, developments in imaging technology and massive accumulation of data, dramatic improvements became possible in percutaneous image-guided tissue sampling (PITS).

PITS is a safe, well-established, and high-yield technique. With the increasing understanding of the molecular biology and the recent emergence of the individualized targeted treatment, molecular profiling appeared as an important tool for individualized treatment. This factor may also have a potential to increase the role of tissue sampling in the future [2–4].

PITS may be performed as a fine needle aspiration (FNA) biopsy (FNAB) or core biopsy (CB) (Fig. 31.1). In FNAB small size, thin needles are used (22 gauges or smaller), whereas in the CB technique large diameter cutting needles (20 gauge and larger) are used for tissue sampling. These techniques can be used separately or combined in the same biopsy session. Most interventional radiologists prefer the coaxial biopsy technique, which involves the initial placement of a thin-walled needle in or close to the target lesion, and subsequent FNA and cutting needle core biopsies can be performed through this needle. By using this technique, the operator does not need to traverse

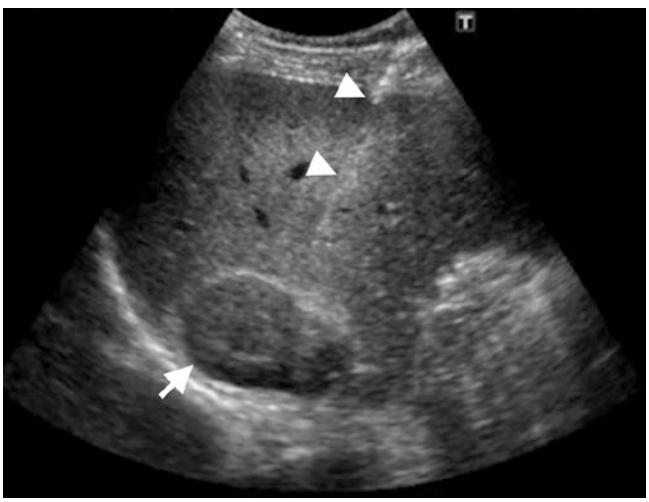


Fig. 31.1 A 54-year-old female with known breast cancer and newly detected focal liver mass (arrow) on follow-up abdominal computed tomography (CT). Percutaneous needle biopsy (arrowheads) of the lesion under ultrasound guidance confirmed metastatic breast cancer

A. D. Karaosmanoglu · M. R. Onur · O. Akhan (✉)
Department of Radiology, Hacettepe University, School of Medicine, Sıhhiye, Ankara, Turkey
e-mail: akhano@tr.net

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_31

the anatomic structures along the trajectory to the target lesion, and therefore, patient discomfort and complication rates can be minimized. FNABs can be performed safely and provide specimens that are adequate for cytologic and histologic examination [2–4]. Cutting needles almost always provide adequate tissue specimens suitable for histopathologic evaluation without increasing complication rates [5, 6].

There are no absolute contraindications for PITS, but a thorough pre-procedure patient work-up should be performed before PITS. Relative contraindications include significant coagulopathy, severely compromised cardiopulmonary function or hemodynamic instability, lack of patient cooperation, and pregnancy—the latter in situations where image guidance involves ionizing radiation [7]. PITS is generally a safe procedure with low complication rates when undertaken with adequate patient work-up and in experienced hands. The complications can be broadly subclassified into two subgroups: generic and organ specific. The major generic complications apply to all biopsies including major bleeding, infection, hollow viscus perforation, and unintended organ injury [7, 8]. Clinically significant bleeding is rare and depends on the increased size of the needle, the use of cutting needles, and the vascularity of the organ biopsied [9, 10]. Infection as a complication is rare with adequate patient preparation and attention to the technique. Injury to adjacent organs is also rare, and this type of injury will require additional intervention in less than 2% of the patients [7]. Major complications result in hospital admissions, unplanned increase in the level of care, long-term morbidities, or death. Minor complications do not have any sequela and may require nominal therapy or short hospital stay, generally overnight, for observation [7].

Biliary Interventions

Obstructive jaundice is a manifestation of cholestasis. By definition, cholestasis denotes either impairment in the formation of bile or obstruction of the free flow of bile to the duodenum along the internal and external biliary ducts. Primary and secondary tumors of the liver, pancreas, and the biliary systems are the commonest causes of biliary obstruction. Malignant biliary obstruction (MBO) may also lead to fatal liver insufficiency and cholangitis [11].

Percutaneous intervention for MBO may be performed to decrease serum bilirubin levels to facilitate the delivery of certain chemotherapy agents, or in some cases to allow for definitive or palliative surgery. Cholangitis is relatively rare in the setting of MBO and should be considered in patients who underwent previous endoscopic or percutaneous intervention [12, 13]. Fever, right upper quadrant pain, worsening hyperbilirubinemia, mental status changes, and sepsis may be the clinical manifestations of cholangitis. In patients with altered biliary anatomy, percutaneous biliary drainage may be the only nonsurgical option for palliative or definitive treatment. Biliary interventions are mostly performed as multi-stage procedures. For most patients, biochemical liver function indices improve after the first intervention [14].

Biliary drainage may be performed as an external or external/internal drainage. In external drainage, the draining catheter is placed proximal to the level of MBO, whereas in external/internal drainage, the catheter is placed across the level of MBO. Electrolyte and fluid disturbances, coagulopathy, and malnutrition may complicate external biliary drainage [15, 16]. For these reasons, the external biliary drainage should be converted to external/internal drainage whenever possible. These drainage catheters should be carefully supervised during their stay in the biliary system and should be exchanged every 2–3 months.

In patients with biliary drainage catheters that were placed for malignant obstruction, cholangitis rates are relatively high and may be seen in up to 50% of the patients with external/internal biliary drainage catheters; the likelihood of infection is directly correlated with the length of the stay of the catheter [4]. Therefore, patients who have biliary drainage catheters in place should have clear treatment plans and precisely defined goals, and the use of metallic stents should not be delayed in patients who are not operative candidates. These stents improve the patient comfort by removing the catheter exiting the patients' skin. These metallic stents have high patency rates for 6–9 months and should be liberally used in patients with limited life expectancy [17, 18] (Fig. 31.2).

Before any biliary intervention, a detailed clinical work-up is necessary. The patient's overall clinical status should be reviewed and the relevant laboratory tests should be performed. Patients' coagulation parameters should be carefully evaluated and treated, if necessary. Pre-procedural antibiotic use with adequate hydration is also crucial for successful outcome. Anesthesia may be consulted in complicated cases.

There should be clear orders for the floor staff after stent placements, as patients may experience pain and fever. Antibiotics may be used for 48 hours after stent placement with adequate pharmacotherapy for pain control.

Urologic Interventions

Urinary obstruction due to malignant causes is not rare, and urinary diversion should be performed in these patients in order to prevent obstructive uropathy and permanent renal damage. Despite the fact that urologic interventions are gen-

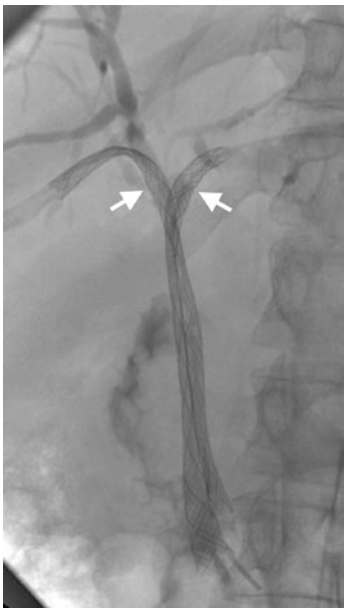


Fig. 31.2 A 61-year-old female with hilar cholangiocarcinoma deemed to be unresectable after clinical and radiological evaluation. Metallic biliary stents (arrows) are percutaneously placed into the left and right biliary ducts in Y-configuration for palliative purposes

erally required in the treatment of urinary tumors and stone diseases, gastrointestinal cancers may also cause acute or chronic urinary obstruction necessitating percutaneous interventions. Major causes of urinary obstruction include pelvic and retroperitoneal masses.

Percutaneous nephrostomy (PCN) is the most commonly applied procedure for the relief of malignant urinary obstruction that cannot be managed by placing a ureteric stent via cystoscopy [19, 20]. As uninfected obstructed kidney is not an acute threat, PCN placement is an urgent procedure rather than an emergent one. Elevated urinary pressure in urinary obstruction leads to afferent arteriolar vasoconstriction with subsequent permanent functional loss through a combination of ischemic or disuse-induced tubular injury [21, 22]. Complete renal function recovery may be expected with 1 week of complete obstruction with very little recovery seen after 12 weeks of complete obstruction [23].

PCN placement is a relatively safe procedure in appropriately selected patients. The major and minor complication rates are reported to be around 10%, with a mortality rate of 0.05–0.3% [20, 24]. Infection, adjacent organ injury, and bleeding are among the major complications of PCN. Pleura and colon are the most commonly injured organs, however, with proper technique the majority of these injuries may be prevented. Minor hematuria and bleeding from the newly placed PCN catheter are very common and mostly transient.

Percutaneous Ablative Therapies

Percutaneous ablative therapies involve application of thermal and nonthermal energy to treat cancer under imaging guidance. Percutaneous ablation is commonly used for the treatment of primary and metastatic tumors in the liver or lung. They can also be used for palliative purposes in bone and soft tissue and lymph metastases.

Thermal ablative technologies include radiofrequency ablation (RFA), microwave ablation, and cryoablation. Proper pre-procedure work-up including a patient's overall clinical and laboratory evaluation is mandatory. Tumor location is also critical and should be evaluated. Tumors that abut pancreas, bowel segments, abdominal wall, and gallbladder necessitate extra attention as collateral damage to these structures may complicate the ablation procedure. With the use of hydrodissection and patient positioning, in addition to careful technique, most of these tumors may be successfully treated without any collateral damage to the adjacent organs.

Radiofrequency Ablation

RFA technology involves application of lethal heat to the tumors by using alternating electrical current. The resulting frictional heat and movement of electrons within the tumoral tissue and surrounding structures cause immediate coagulative necrosis and cell death. In addition to its use in primary liver tumors, especially hepatocellular carcinoma, it is also widely used in the treatment of metastatic liver disease. This heat energy is typically delivered by inserting the RFA probe into the tumor under imaging guidance. The size and the configuration of the ablation zone can be modified with the type and numbers of the electrodes, the duration of ablation, and inherent tissue characteristics [25]. With its proven efficacy and safety profile, RFA is now offered to patients who are surgical candidates with comparable 5-year survival outcomes from surgical intervention [26–29]. Several points should be addressed during the pre-procedural work-up in patients who are planned to be treated with RFA. Metastatic lesions close to large-caliber hepatic vessels may induce a heat-sink effect, wherein the thermal energy applied is attenuated by the blood flow in these large vessels. Large tumor size is another limiting factor, and lesions larger than 5 cm may be difficult to treat with this technology. Attention should be paid to adjacent organs as injuries to gallbladder and intestinal loops adjacent to the ablation site may be devastating [4]. RFA, with its long record of success and availability, is a very attractive technology in the treatment of metastatic and primary tumors in several organs, and patients may even be discharged at the day of ablation after some

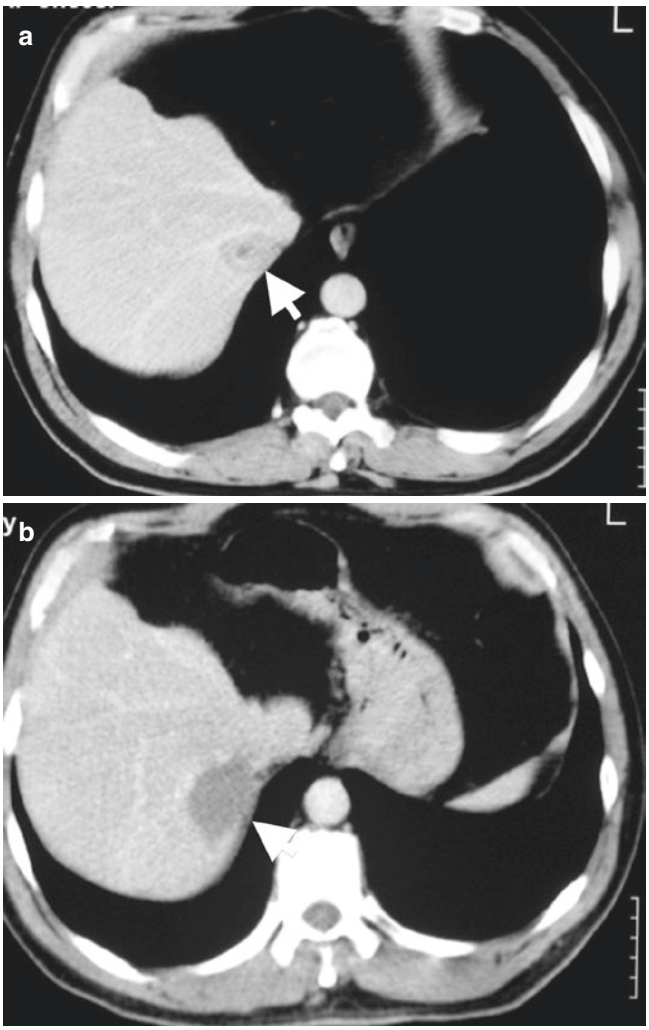


Fig. 31.3 Radiofrequency ablation of liver metastasis. A 52-year-old male with newly diagnosed solitary liver metastasis due to colon cancer. Patient refused liver resection. (**a**) Pre-RF ablation contrast-enhanced computed tomography (CT) image reveals low-attenuation metastatic lesion (arrow) adjacent to the inferior vena cava. (**b**) Post-ablation CT image demonstrates no abnormal enhancement (arrow) within the ablation bed suggestive of residual tumor

observation at interventional radiology recovery suites (Fig. 31.3a, b).

Microwave Ablation

Another thermal-based ablative technology is microwave ablation (MWA). This technology is relatively new compared to RFA and is highly promising. MWA promotes heat production through a specifically designed antenna and causes polar water molecules to realign continuously with an oscillating magnetic field generated from the antenna. This continuous realignment of the water molecules produces friction and subsequent heat, inducing coagulative necrosis and cell death [30]. By using MWA several shortcomings of RFA may be circumvented. Low electrical conductivity and high tissue impedance—a common problem in charred tissues treated with RFA—do not affect the propagation of microwaves, and therefore an increased treatment effect may be obtained with MWA [31]. Heat-sink effect, a common limiting factor in RFA, is also not a problem with the MWA technology. The thermal profile generated by the MWA technology overcomes the heat-sink effect, allowing the treatment of lesions located close to the large-caliber hepatic vessels. MWA also allows application of multiple probes at the same time into different lesions, which may significantly reduce the treatment duration [32]. The grounding pads, mandatory to use in RFA, are also not needed with MWA. The active heating zone is larger in MWA compared to RFA, which reduces the charring and desiccation seen in RFA. As a result of this feature of MWA, a more uniform ablation zone is achieved within a shorter duration [30, 33, 34] (Fig. 31.4a–d).

Cryoablation

Cryoablation differs in the way the thermal ablation is achieved. In this technology, instead of heating, rapid cooling of the tumor tissue is used for ablation. Cryoablation is based on the Joule Thomson effect, which is based on the high-pressure travel of the gas through a porous plug into an area of lower pressure with subsequent cooling and expanding of the gas. The cold temperatures obtained with cryoablation causes intracellular and extracellular ice and crystal formation within the tissue, followed by direct destruction of the cellular membranes and subsequent cell death [32]. Cryotherapy has been reported to be effective for tumors with a size less than 5 cm in diameter, but with the utilization of multiple probes, tumors up to 10 cm in diameter may now be treated [35]. The iceball that is formed during the treatment cycle can be clearly visualized with imaging, which confers an advantage as the treatment zone can be real-time monitored during the treatment session. Abscess, tumor seeding, liver cracking, cryoshock, and hemorrhage may complicate cryoablation; however, no significant differences have been described between RFA and cryoablation in trials comparing these two techniques [36].

Irreversible Electroporation

Irreversible electroporation (IRE) is the newest ablation modality, despite the fact that the idea behind this technology dates back to the 1960s [37]. The usefulness of IRE as an ablation modality was first described in 2005 where its abla-

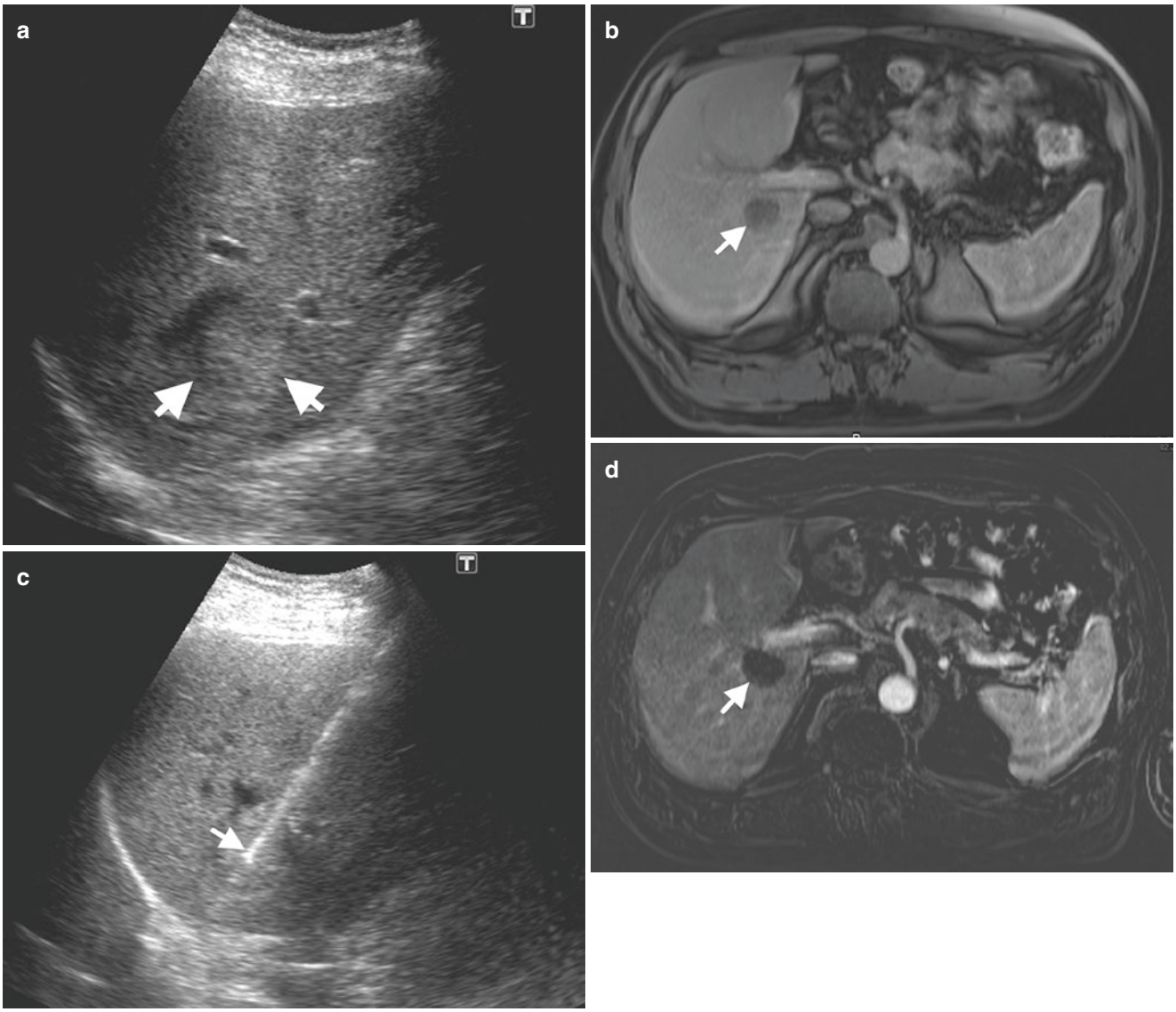


Fig. 31.4 Microwave ablation of liver metastasis. A 45-year-old male with biopsy-proven solitary metastatic focus within the liver parenchyma secondary to colon cancer. Patient refused surgical resection of the metastasis. (**a**) Grayscale ultrasound (US) image shows heterogeneously hyperechoic solid metastasis (arrows). (**b**) Pre-treatment contrast-enhanced axial magnetic resonance (MR) image confirmed the US findings (arrow) and did not demonstrate any additional metastatic foci. (**c**) Grayscale sonographic image shows the properly positioned microwave antenna (arrow) within the metastasis. (**d**) Posttreatment subtraction MR image revealed no abnormal enhancement within the ablation bed (arrow) consistent with successful treatment

tive effect was demonstrated in the liver tissue without thermal effects [38]. The killing effect of IRE is based on the ability of high electric field strength causing permanent pore formation within the cell membrane, resulting in cell death [39]. As IRE is based on nonthermal ablation, the heat-sink effect, most commonly observed in tumors adjacent to major blood vessels, is not a limiting factor [40]. IRE also does not significantly affect the connective tissue elements allowing its use in the treatment of tumors in the close vicinity of sensitive structures, such as nerves and bile ducts, without any serious long-term effect [40–43]. The major limitation of IRE is the requirement of general anesthesia during the procedure, as complete muscle paralysis is required to reduce muscle stimulation during the treatment. Even with complete muscle blockade, local muscle stimulation is common. An electrocardiogram synchronizer is also necessary to minimize the risk of cardiac rhythm disturbances during the procedure [39]. IRE can be used in the treatment of kidney, liver, pancreas, and lung ablations, but the results in ablating pancreatic cancers are especially promising [39] (Fig. 31.5a–c). As IRE is a relatively new ablation technology in the treatment arsenal, there are some knowledge gaps, and more experience and scientific data are needed before it becomes mainstream.

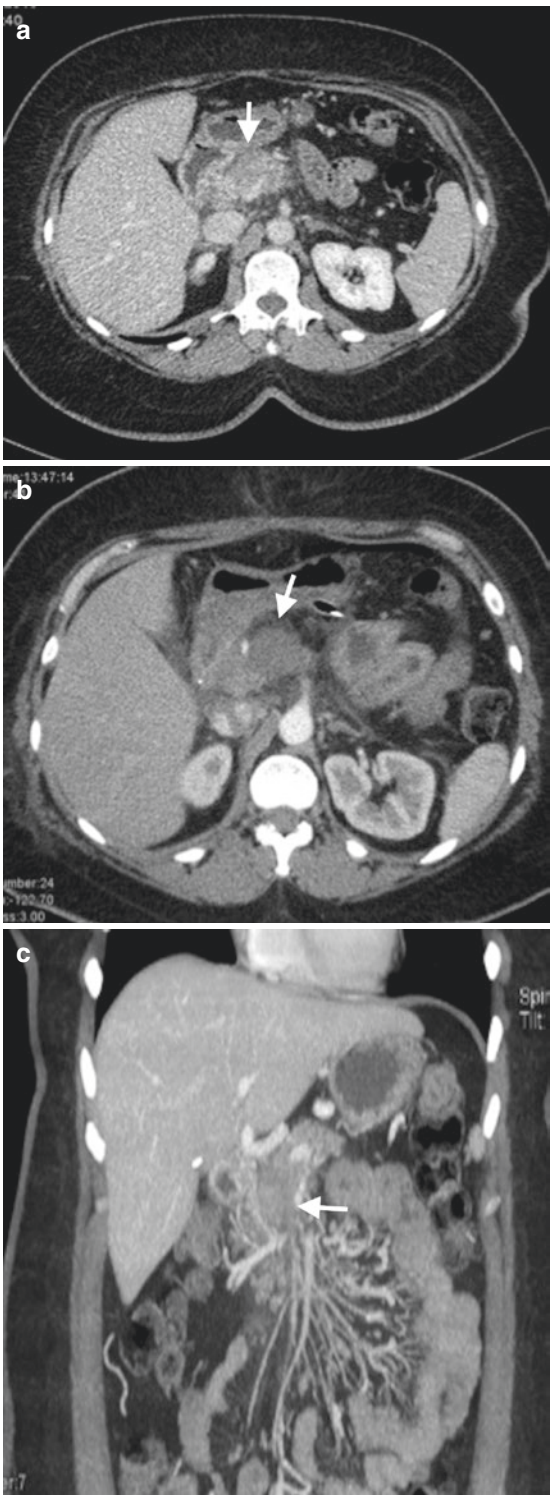


Fig. 31.5 Irreversible electroporation (IRE) of pancreatic cancer. A 67-year-old male presenting with gradually increasing epigastric pain and weight loss. (**a**) Axial contrast-enhanced computed tomography (CT) demonstrated pancreatic head mass (arrow) that was later proven to be consistent with adenocancer after endosonographic biopsy. The lesion was deemed to be unresectable with extensive vascular invasion. Post-IRE treatment axial (**b**) and coronal (**c**) contrast-enhanced CT images show satisfactory treatment with expected morphologic changes represented by devascularization of the tumor (arrows)

Hydrodissection

Hydrodissection is a very useful technique in ablative therapies for lesions located close to critical anatomic structures. This technique basically involves creation of artificial ascites, which displaces the adjacent organs away from the tumor itself. A 5% dextrose in water solution should be used in RFA patients, as normal saline may act as an electrical conductor and can propagate ablation [44]. In case the hydrodissection fluid is difficult to visualize with computed tomography (CT), iodinated contrast may be added to the fluid [45].

Comparison of Percutaneous Ablation Technologies

With the advance in percutaneous ablative technologies the selection of the correct modality is becoming crucial. With the refinement in these technologies, the success of treatments will increase with diminishing complication rates. As the RF technology improves, the efficacy of this technology appears also to be improved for ablating larger tumors, now reported to be around 80–90% [46]. Ablative technologies based on microwave are less vulnerable to heat-sink effects from adjacent vessels and may be more useful to treat lesions adjacent to large caliber vessels. As IRE is a nonthermal ablative technology, there is no concern for heat-sink effects, and it enables better tumoricidal effect with less risk to damage adjacent vascular and biliary structures. Based on these potential advantages of IRE, it will not be surprising to see its use in liver tumors in the near future. Because of high complication rates and lack of solid scientific data regarding its advantages over other ablative modalities, the utilization of cryoablation for liver applications is still limited.

Portal Vein Embolization

Hepatic resection is the standard of care for patients with primary and secondary liver malignancies. However, despite the advancements in pre-, peri-, and post-surgery care, significant complications such as cholestasis, liver failure, synthetic liver dysfunction, and fluid retention are still important factors that affect patient morbidity and mortality.

Liver insufficiency is a potentially lethal complication of the liver resection, and the volume of future liver remnant (FLR) is the main determinator of postsurgical hepatic dysfunction and complications [47–49]. The rationale of portal vein embolization (PVE) is to increase the volume of FLR by redirecting the blood flow in the portal vein toward the FLR by embolizing the portal vein branches feeding the liver seg-

ments that will be removed at surgery. With this redirection of blood flow, the nonembolized liver segments will hypertrophy with the aim of reducing the risk of potential postoperative liver insufficiency, thereby increasing the number of patients eligible for surgery [50, 51] (Fig. 31.6a–e).

Adequate pre-procedural planning, as is usual, is mandatory for the success of PVE. Cross-sectional imaging with multiphasic abdominal CT or liver magnetic resonance imaging (MRI) may both be used for this purpose. With the information provided from these studies, the total liver volume, the FLR volume, and anatomy of the portal vein and its

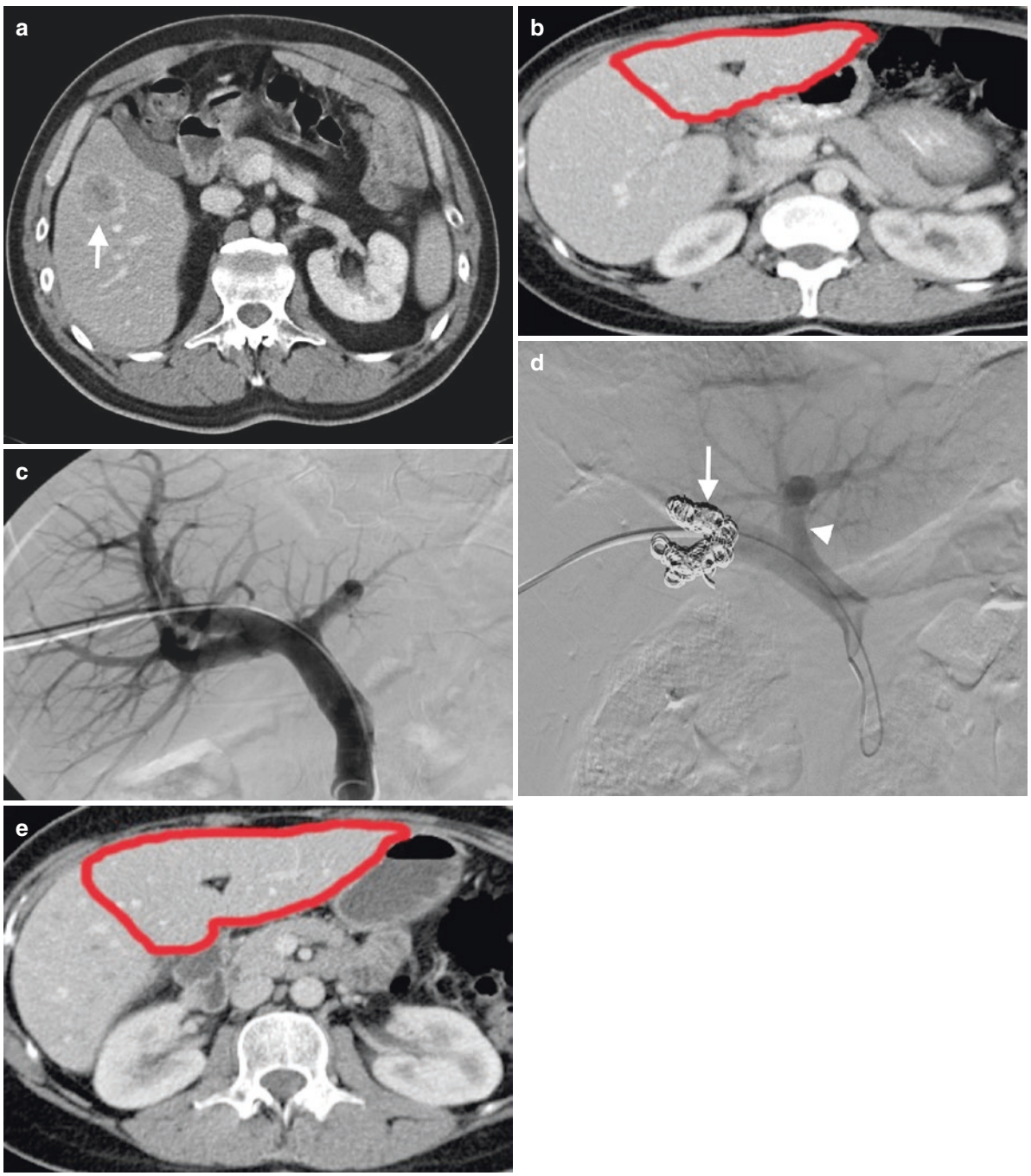


Fig. 31.6 Portal vein embolization (PVE) in a 57-year-old male patient with right lobe liver metastasis due to colon cancer. (**a**) Axial contrast-enhanced computed tomography (CT) demonstrates the largest metastatic lesion in the right lobe (arrows). No metastatic lesion was detected in the left liver lobe. (**b**) Axial contrast-enhanced CT before the procedure showing left liver lobe. (**c**) Pre-embolization portal venography demonstrates patent portal vein branches and outlining the anatomy. (**d**) Post-embolization portal venography demonstrates successful embolization of the right portal vein branches (arrow) and patent left portal vein (arrowhead). (**e**) Axial contrast-enhanced CT 4 weeks after PVE demonstrates satisfactory enlargement of the left liver lobe

branches can be thoroughly evaluated. The diameter and distal branches of the portal vein, in order to gain safe access, should also be evaluated in these images.

As stated previously, the amount of remnant liver volume is crucial for patient well-being after the surgery. Guidelines state that PVE may be indicated in patients with anticipated FLR of ≤20% in healthy livers, ≤30% in diseased livers or those with chemotherapy-associated steatohepatitis, and ≤40% in cirrhotic livers [52, 53].

Several studies have reported that FLR standardized to patient size may be a reliable indicator for estimating functional liver volume. This is calculated from the data provided by CT volumetry measurement of FLR and calculating its contribution to the total liver volume as a proportion of estimated liver volume derived from the patient's body surface area [54].

Significant portal hypertension, extensive or partial tumor invasion of the portal vein and complete lobar portal vein occlusion, renal failure, uncorrected coagulopathy, extrahepatic metastases, and absence of a safe access route to the portal vein are the leading absolute and relative contraindications for PVE.

PVE is a safe procedure, which can be performed under conscious sedation, with high success rates. The reported hypertrophy rates of FLR range from 28% to 46% [4]. A systematic review assessing the results of 44 articles, overall including 1791 patients who underwent PVE, demonstrated a mean hypertrophy rate of 37.9 ± 9%, a success rate of 99.3%, and a mortality rate of 0.1% [55].

Transarterial Treatments of Liver Tumors

Primary and secondary malignancies of liver are amenable to transarterial treatment approaches due to their unique preferential blood supply from hepatic artery rather than portal vein branches. Bland embolization with particles, embolization with drug-loaded particles and transarterial delivery of yttrium-90 (Y-90)-coated microspheres are all available in the interventionalist's arsenal for different indications.

Transarterial Chemoembolization

For transarterial chemoembolization (TACE), a chemotherapeutic drug is added to the embolic agent. With this combination, a synergistic treatment effect with both tumor embolization and controlled, focused release of the drug can be obtained. Doxorubicin and cisplatin are the most commonly used chemotherapeutic agents in this treatment; however, several other agents may also be used if needed.

The development of polymer-based drug-eluting microspheres (drug-eluting beads, DEBs) has significantly improved the ability of conventional TACE. With this technology, the chemotherapeutic agent can be delivered at higher concentrations locally with decreased systemic toxicity [56] (Fig. 31.7a–c). Most of the data in the literature were generated with the use of DC beads produced by Biocompatibles/BTG in the UK [57]. These beads can be loaded with doxorubicin (DEBDOX) or irinotecan (DEBIRI) [58, 59]. These beads are non-biodegradable, spherical shaped, and compressible particles that can be loaded with doxorubicin or irinotecan with a size range of 75 to up to 900 microns. The drug release is gradual and continuous, as demonstrated in several animal experiments [56, 60]. Small bead size allows for deeper penetration of the particle and more extensive necrosis [61]. However, it should be underlined that smaller particles are not always better. Serious complications with 40–120 micron trisacryl spherical microspheres due to nontarget embolization have been reported due to the passage of these small particles through sinusoids and large arteriovenous shunts located within the target tumor [62].

Metastatic colorectal cancer (mCRC) to the liver is a significant cause of mortality in colorectal cancer patients. Although surgery is the standard of care for these patients, unfortunately, many patients are not eligible for potentially definitive surgery. TACE with drug-eluting beads may be used in these patients as a palliative procedure. A life expectancy greater than 3 months and an appropriate health status (Eastern Cooperative Oncology Group status of 2 or less) is typically indicated before the treatment [63, 64]. Adequate liver reserve is also mandatory for the success of the procedure. Serum bilirubin less than 3 mg/dL, international normalized ratio (INR) of 1.5 or less, and albumin greater than 3 g/dL are typically good indicators of adequate liver reserve [65]. Pre-procedural abdomen CT or MRI is also needed, ideally within less than 1 month before the procedure. TACE may be performed with doxorubicin or irinotecan, and several combinations of TACE with surgery and systemic chemotherapy have been reported in these patients with differing results [66].

The use of TACE in other liver metastases except for mCRC to the liver has also been reported, but the data are scarce in these patients. The use of TACE in these patients, especially in patients with liver metastases due to neuroendocrine tumors, appears to be promising [67–71]. Local disease control and symptomatic relief may be obtained with TACE in these patients.

Hepatocellular carcinoma (HCC) is the 6th most common cancer and 3rd leading cause of cancer deaths [72]. Embolization of HCC was first performed by a French radiologist, Dominique Doyon, in 1974 with the use of gelatin as the embolizing agent [73]. Lipiodol was first reported by Japanese surgeon Kono as a bounding and accumulating agent in HCC [72]. In the first clinical study conducted in 1983, significant reduction in serum alpha-fetoprotein (AFP)

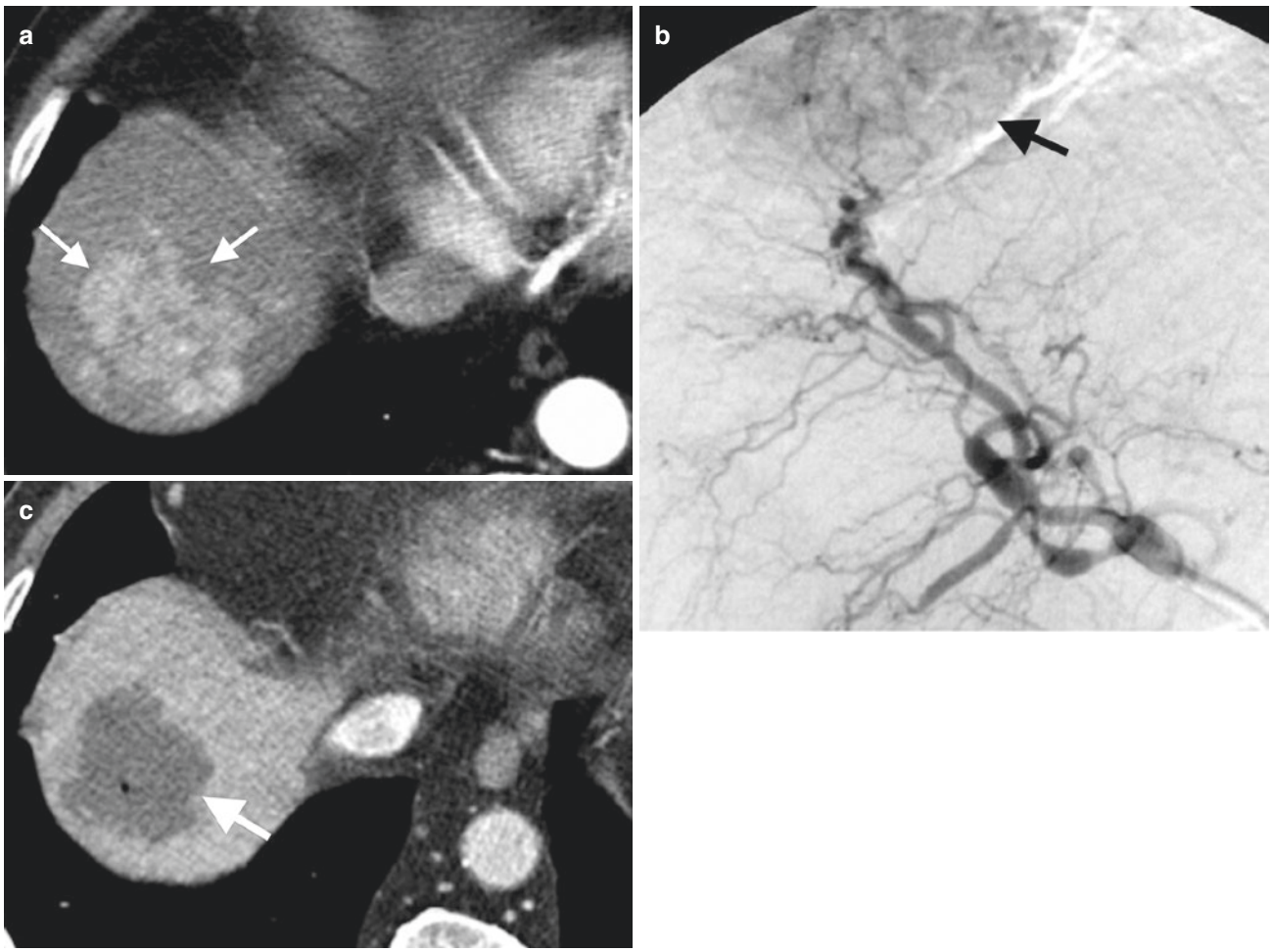


Fig. 31.7 Transarterial chemoembolization in a 56-year-old male with known cirrhosis secondary to chronic hepatitis C virus infection. (**a**) Arterial phase contrast-enhanced computed tomography (CT) demonstrates avidly enhancing lesion (arrows) in the liver dome suggestive of hepatocellular carcinoma. The same lesion demonstrated contrast wash-out on portal venous phase (not shown). (**b**) Pre-embolization catheter angiography demonstrated the same hypervascular lesion (black arrow) seen on CT images. (**c**) Axial contrast-enhanced CT 4 weeks after chemoembolization demonstrates almost complete tumor response with no enhancement within the tumor tissue (arrow)

levels have been reported in HCC patients who are treated with TACE [74].

The target population for TACE procedure are stage B (intermediate stage) patients, according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Relatively preserved liver function, absence of cancer-related symptoms, no evidence of vascular invasion or extrahepatic spread, and Child-Pugh stage of $\leq$ B7 are the preferred conditions for optimal TACE procedure [75–78]. TACE may also serve as an alternative for patients with early-stage HCC, when other more commonly used treatment options cannot be performed. Patients with advanced liver dysfunction are not ideal candidates for TACE procedure as severe adverse effects may be observed due to ischemic effects of this procedure. Absolute contraindications for TACE include decompensated cirrhosis (Child-Pugh stage $\geq$ B8), extensive tumor involvement with massive replacement of both lobes, severely reduced portal vein flow (with or without tumor obstruction), technical contraindication to intra-arterial treatment and severe renal impairment (serum creatinine >2 mg/dl or creatinine clearance <30 mg/dl) [79]. Relative contraindications are as follows: tumor size >10 cm, severe comorbidities, esophageal varices with high risk of bleeding and bile duct occlusion, or incompetent papilla due to stent or surgery [79].

Long-term survival is unusual after TACE procedure as these patients mostly have advanced stage tumors. Interruption of the tumor blood flow may also lead to enhanced angiogenesis, which may promote new tumor formation [80]. Hypoxia inducible factor 1 α(alpha) and both plasma and hepatic vascular endothelial growth factor (VEGF) levels were reported to increase after TACE [80]. Combined use of anti-angiogenetic agents with TACE was proposed as alternative to overcome this potential drawback [81].

Pre-treatment imaging of TACE should include properly protocolled CT or MRI exam for initial assessment of the hepatic tumor load. Extrahepatic metastatic disease should also be ruled out before the procedure. The most commonly preferred drug for TACE, in patients with HCC, is doxorubicin mixed with lipiodol. Doxorubicin can be used with a dose of 30–75 mg/m^2, not exceeding 150 mg [82]. Doxorubicin-eluting beads (DEB)-TACE limited disease, according to Milan criteria, is defined as follows: single HCC ≤5 cm or multiple tumors (up to 3 at ≤3 cm each) [80]. Patients who successfully meet the Milan criteria may be treated with a planned dose of 50–75 mg doxorubicin loaded into one vial of 2 mL of DC beads (per single session). In patients with advanced stage disease, single treatment session should include a dose of up to 150 mg doxorubicin loaded into two vials of DC beads. Huge or bi-lobar tumors necessitate separate sessions with ~4 weeks apart [82]. In case of complications related to the procedure, the interval between the sessions may be extended. Before the subsequent procedure, liver functions should be thoroughly evaluated.

Complications of TACE

TACE-related mortality within 1 month was reported to be at 4% in the PRECISION V study. In this study acute hepatocellular failure (>60% of cases), hemorrhage due to portal hypertension, tumor rupture, liver abscess, and sepsis were reported to be the most common causes of TACE-related mortality [83]. Ischemia of nonmalignant liver parenchyma is among the leading causes of adverse effects that may manifest as increased serum bilirubin levels, encephalopathy, reduced prothrombin ratio, and rupture of varices [78]. Among the less common complications of TACE are cholecystitis, biliary tract-related complications (such as bilomas, stenosis, and dilatations), pancreatitis, and bowel perforation [84].

Response Assessment After TACE

Response evaluation criteria (RECIST) may not be relevant for the assessment of tumor response after TACE as overall decrease in tumor size may not reflect the true response [85]. Modified RECIST (mRECIST) was proposed to be better for response assessment in TACE of HCC [86, 87].

Response evaluation after TACE should be performed with properly protocolled contrast-enhanced CT or MRI, typically 4 weeks after the index session [77] (Fig. 31.8a, b). Re-treatment at subsequent fixed intervals may be planned for future management. Repeated TACE sessions may be related with higher toxicity [79]. On-demand strategy refers to re-treatment of patients if viable tumor tissue remains (partial response, stabilization, or progression) and can be carried out depending on the patient's liver reserve and overall health [78]. Three-month interval follow-up imaging is recommended for patients with complete response. Failure to achieve an objective imaging response after at least two sessions, clinical or functional deterioration, and interval development of usual factors that contraindicate TACE procedure are considered to be factors supporting for the TACE untreatable disease progression [78]. Absence of response after at least two TACE sessions should prompt consideration for alternative treatment approaches [79, 88]. Average number of TACE sessions per patient was reported to be as 2.5 ± 1.5 [85].

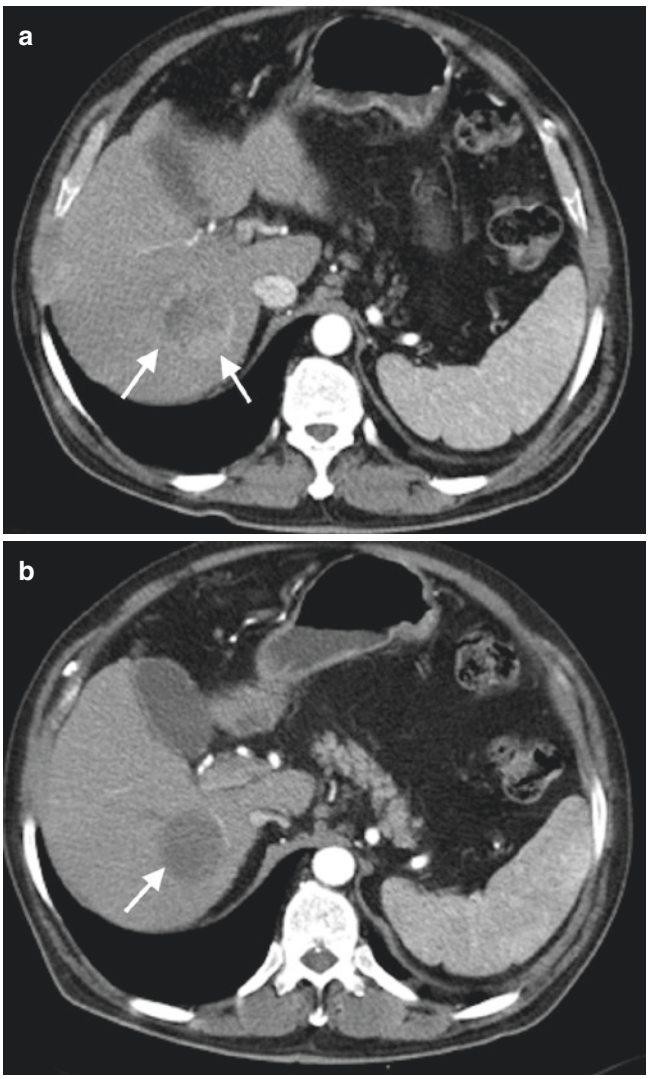


Fig. 31.8 TACE in a 70-year-old man with HCC. (**a**) Arterial phase axial contrast-enhanced CT demonstrates peripherally avidly enhancing lesion (arrows) in the right lobe of the liver pathologically proven as hepatocellular carcinoma. (**b**) Arterial phase axial contrast-enhanced CT performed 1 month after DEB-TACE procedure revealed unenhancement of the lesion (arrow) suggestive of complete tumor response

Outcomes

Proper patient selection is of fundamental importance for successful clinical outcome. Conventional TACE procedures were shown to be more beneficial for patients who are not amenable for more radical treatment approaches [80].

DEB-TACE has been shown to be more valuable compared to conventional TACE in HCC. The PRECISION V study, a multicenter phase 2 randomized trial, revealed superiority of DEB-TACE with doxorubicin-eluting beads. This approach resulted in less liver toxicity and drug-related adverse events [89, 90]. Higher complete response, objective response, and disease control rates were reported to be as 27% vs. 22%, 52% vs. 44%, 63% vs. 52% in DEB-TACE group and cTACE group, respectively [91]. Complete tumor necrosis was observed in 77% of patients with DEB-TACE as compared to 27% in bland embolization [92]. However, superiority of DEB-TACE over cTACE is not well-established due to lack of solid scientific evidence. The GIDEON study is an observational registry study that evaluated the TACE use prior to and concomitantly with sorafenib in patients with unresectable HCC. In this study, overall survival was 12.7 months in patients who underwent TACE prior to sorafenib; 9.2 months in non-prior-TACE patients; and 21.6 months and 9.7 months in concomitant and non-concomitant-TACE patients, respectively [93].

Some recent TACE studies have been ongoing with novel beads, which are small particles leading to more distal embolization. These smaller particles also allow for embolizing the newly formed collateral vessels from prior sessions [94, 95]. Concerns about extrahepatic embolization and toxicity due to collateral circulation have not been validated [96]. A prospective study revealed complete and partial response in 33.3% vs. 44.4% of patients, respectively, with DEBs of 70 μ(mu)m vs. 150 μ(mu)m (M1®, BTG, United Kingdom) [97]. Another novel drug-eluting particle is HepaSphere, which is a microsphere having a dry caliber of 30–60 μ(mu) mol/L. This particle expands to 166–242 (197 ± 31) μ(mu) mol/L in saline solution and to 145–213 (148 ± 45) μ(mu) mol/L after loaded with doxorubicin [98]. Complete response and objective response rates (complete response + partial response) were found to be as 22.2% and 68.9%, respectively [99].

Post-embolization Syndrome

Post-embolization syndrome (PES) is common after liver-directed therapies, especially TACE. It is generally a benign process and can be managed effectively. Nausea, vomiting, abdominal pain, and fever are common after TACE and may be seen in up to 90% of the patients [100]. Intravenous fluid resuscitation and pain management are the mainstays of treatment, but the symptoms may continue up to a week or 10 days.

TACE with the use of DC beads appears to have increased tolerability with a significant reduction in liver toxicity and doxorubicin-related side effects compared to conventional Lipiodol-based TACE [89].

Selective Internal Radiotherapy with Y-90

External beam radiotherapy has historically played a limited role in the treatment of liver tumors as the liver tissue is not tolerant to high-dose radiation. Liver radiation doses exceeding 35 Gy typically cause a clinical syndrome characterized by hepatomegaly, elevated liver enzymes, and ascites. These symptoms may be persistent and recovery may take weeks or even months [101–103]. These limitations have promoted a search for a better and more tolerable way of high-dose radiation delivery to liver tumors. Y-90 has emerged as a feasible molecule to achieve this effect. By definition, radioembolization refers to injection of embolic particles loaded with a radioisotope by using catheter angiography techniques [63] (Fig. 31.9a–c). Y-90-loaded microspheres can deliver beta radiation to the tumor and provide tumoricidal effects. As stated, Y-90 subsequently decays to stable zirconium 90 emitting beta radiation in the meanwhile and has a physical half-life of 64.2 hours [101]. The mean penetration achieved by the emissions is 2.5 mm with a maximum reach of 11 mm. This limited penetrative capability of these emissions provides local tumoricidal effect without nontarget radiation of the healthy liver tissue, which is a common feature in external beam radiotherapy [104]. With the use of this technique, up to 150 Gy of radiation may be delivered to the liver without any significant radiotoxicity to the liver [63].

There are two commercially available radioembolic devices available. TheraSphere was first approved in 1999 by the US Food and Drug Administration (FDA) under humanitarian device exemption, for treatment of unresectable hepatocellular carcinoma, and is a glass microsphere. The second device, SIR-Spheres, was approved by the FDA in 2002 for the treatment of CRC metastases with adjuvant intrahepatic artery chemotherapy for floxuridine [63]. Combined analysis of three trials of first-line FOLFOX (leucovorin, fluorouracil, and oxaliplatin) chemotherapy with or without selective internal radiotherapy (SIRT) revealed efficacy of SIRT in local disease control [105] (Fig. 31.10a, b). However, the same study revealed that addition of SIRT to first-line FOLFOX chemotherapy in patients with liver-only and liver-dominant metastatic colorectal cancer did not improve overall survival compared with that for FOLFOX alone [106]. Therefore; early use of SIRT in combination with chemotherapy in patients with metastatic colon cancer was not recommended [106].

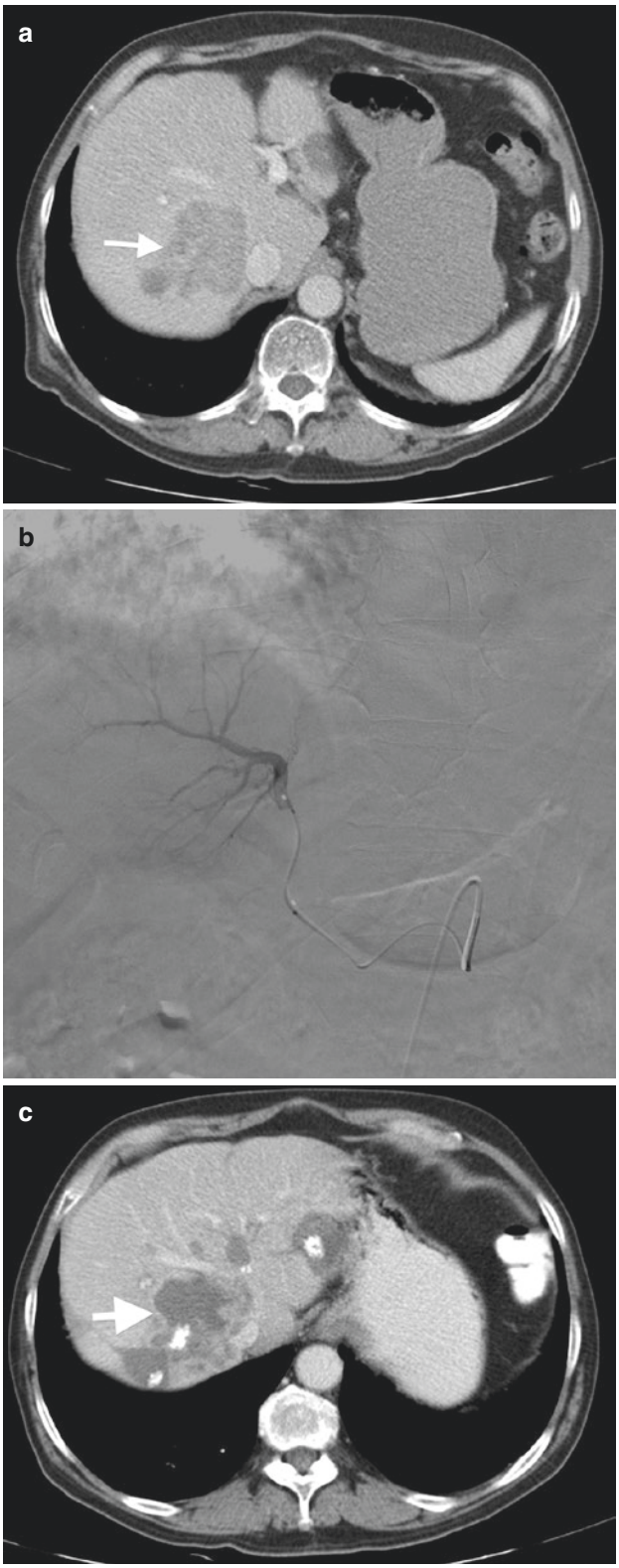


Fig. 31.9 Radioembolization with Y-90. (**a**) Axial contrast-enhanced CT demonstrates solid mass (arrow) close to the liver dome (pathologically proven colon cancer metastasis). (**b**) Y-90 infusion through the right hepatic artery. (**c**) Four weeks after the treatment of the lesion manifested with significant reduction in its vascularity (arrow) consistent with tumor necrosis

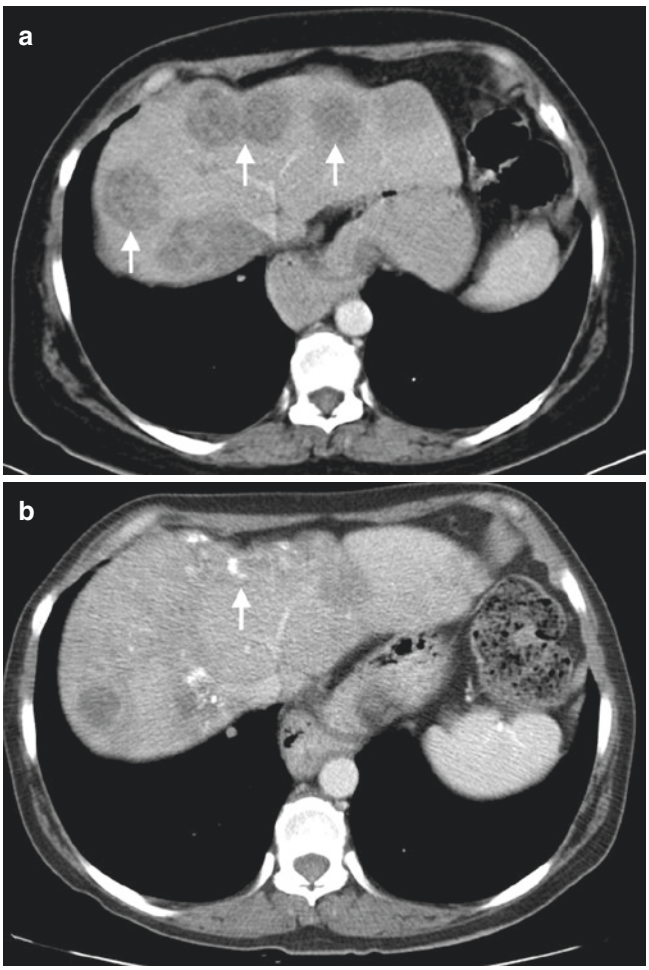


Fig. 31.10 A 54-year-old female patient with multiple liver metastases from breast cancer. (**a**) Axial contrast-enhanced CT demonstrates multiple enhancing metastatic lesions (arrows) in the liver. (**b**) CT examination performed 3 months after SIRT procedure reveals shrinkage of metastases (arrow)

In contrast to TACE, radioembolization is a two-step procedure. The first angiography procedure is performed for vascular mapping and embolization of the vessels that may cause nontargeted internal radiation during the actual radioembolization process. Technetium 99m (Tc 99m)-labeled macroaggregated albumin (MAA) is also injected at this procedure into the target vessel in order to assess fraction of the MAA that shunts to the lungs. This assessment is especially important as significant shunting of the radioembolization particles to the lungs may cause severe radiation pneumonitis after the procedure. The lung shunt fraction is incorporated into the dosimetry calculations to minimize radiotoxicity to the lungs.

Radioembolization can be performed in three ways: whole liver radioembolization, sequential (treating one lobe followed by the other), and lobar (treating only one single lobe of the liver). The decision-making process of selection

of any of these approaches for a given patient is based on the disease burden, distribution, vascular anatomy, and the overall medical condition of the patient. Dosing of the overall radiation may be modified in patients with impaired liver reserve.

PES is milder in radioembolization compared to TACE, and patients may generally be discharged on the same day, in contrast to TACE, wherein patients generally stay overnight for management of PES. Nontarget embolization and subsequent radiation injury is rare and can be minimized with improved technique and careful pre-procedural assessment [107]. The safety and efficacy of internal radioembolization for the treatment of mCRC to the liver have been confirmed in several studies by several groups [66].

As with TACE, several studies have examined the effect of Y-90 internal radioembolization with systemic chemotherapy and reported promising results [66].

5-Fluoro-deoxy-uridine (FUDR) has been extensively used for intraarterial hepatic chemoembolization (IAHC) as the uptake percent of this agent is 95% at the first pass. With this way, 100–300 times higher dose of FUDR may be delivered to the liver when compared to systemic conventional intravenous treatment [66]. All clinical trials using 5-FU or FUDR demonstrated a better response rate for IAHC than for systemic intravenous (IV) treatments. Despite this apparent advantage, only a few trials have demonstrated a benefit of this approach in overall survival [108, 109]. In one randomized trial, a significant survival benefit was reported for patients undergoing continuous hepatic arterial infusion with FUDR compared with the control arm patients who were treated with systemic chemotherapy with 5FU/best medical treatment (BMT) (13.5 versus 7.5 months; $p = 0.03$) [110].

There are only a few absolute contraindications for Y-90 microsphere treatment. Radiation pneumonitis occurs when lung exposure exceeds 30 Gy during treatment. This potential complication can be prevented by pre-procedure preparation angiography performed with 99mTc macroaggregated albumin (MAA). It is important that liver injection of MAA is performed with flow rates and catheter position mimicking the anticipated Y-90 infusion rate and catheter position in the actual treatment session. In patients with vascular anatomy incompatible with safe treatment, radioembolization should also not be performed [111].

Relative contraindications to Y-90 microsphere treatment include limited hepatic reserve, irreversibly elevated bilirubin levels, compromised portal vein (unless selective or superselective radioembolization can be performed), and prior radiation therapy involving the liver [111].

Gastrointestinal Stenting for Palliation of Obstruction

Gastrointestinal stenting is primarily used for palliation approaches or as a means for transition to definitive surgery. The major goal of these stents is to restore and maintain the patency of any obstructed segment of the gastrointestinal system. Since their first use, they underwent significant development from the first rigid stents to today's more flexible and effective stents. In modern practice, expandable plastic and metal stents as well as biodegradable stents are commonly used for maintaining patency in several parts of the gastrointestinal tract [112]. Self-expandable metal stents (SEMS) are the most commonly used stents for this purpose, and they are manufactured from stainless steel and alloys such as Nitinol and Elgiloy or a combination of Nitinol and silicone [112]. In order to reduce in-stent tumor growth and subsequent obstruction, these metals stents may be covered with silicone or a membrane [112].

Stent Use for Esophageal Obstruction

Esophageal cancers (EC) are not uncommon, and, unfortunately, fewer than 50% of the patients are potential candidates for surgical resection. Most of the patients diagnosed with EC are at an advanced stage at the diagnosis, with dysphagia being the most common symptom. Palliation is critical in these patients and stents are commonly used for this purpose.

Covered or uncovered SEMS are commonly used for maintaining the patency of the esophageal lumen (Fig. 31.11a–c). Covered stents are especially useful in patients with malignant fistula formation between the esophagus and the adjacent anatomic structures [113, 114]. Esophageal stent insertion may be combined with brachytherapy as a safe palliative option in patients with EC who are not operative candidates [115].

Covered stents are reported to be more successful in terms of long-term patency and prompt relief of malignant obstruction with significantly reduced requirement for repeat intervention [116]. Anti-reflux stents are also available with complication rates and quality of life similar to those with conventional SEMS; however, further research is needed to confirm these optimistic results [117]. The technology of biodegradable stents is relatively new with its unique advantages. SEMS may interfere with radiotherapy planning and delivery schedule, but biodegradable stents have no such effect and they generally dissolve within 6–8, which generally corresponds to the radiotherapy schedule [118–120]. Stent migration, which may be seen after shrinkage of tumor after chemoradiotherapy, may necessitate an extra procedure for stent removal in patients with metallic stents. However,

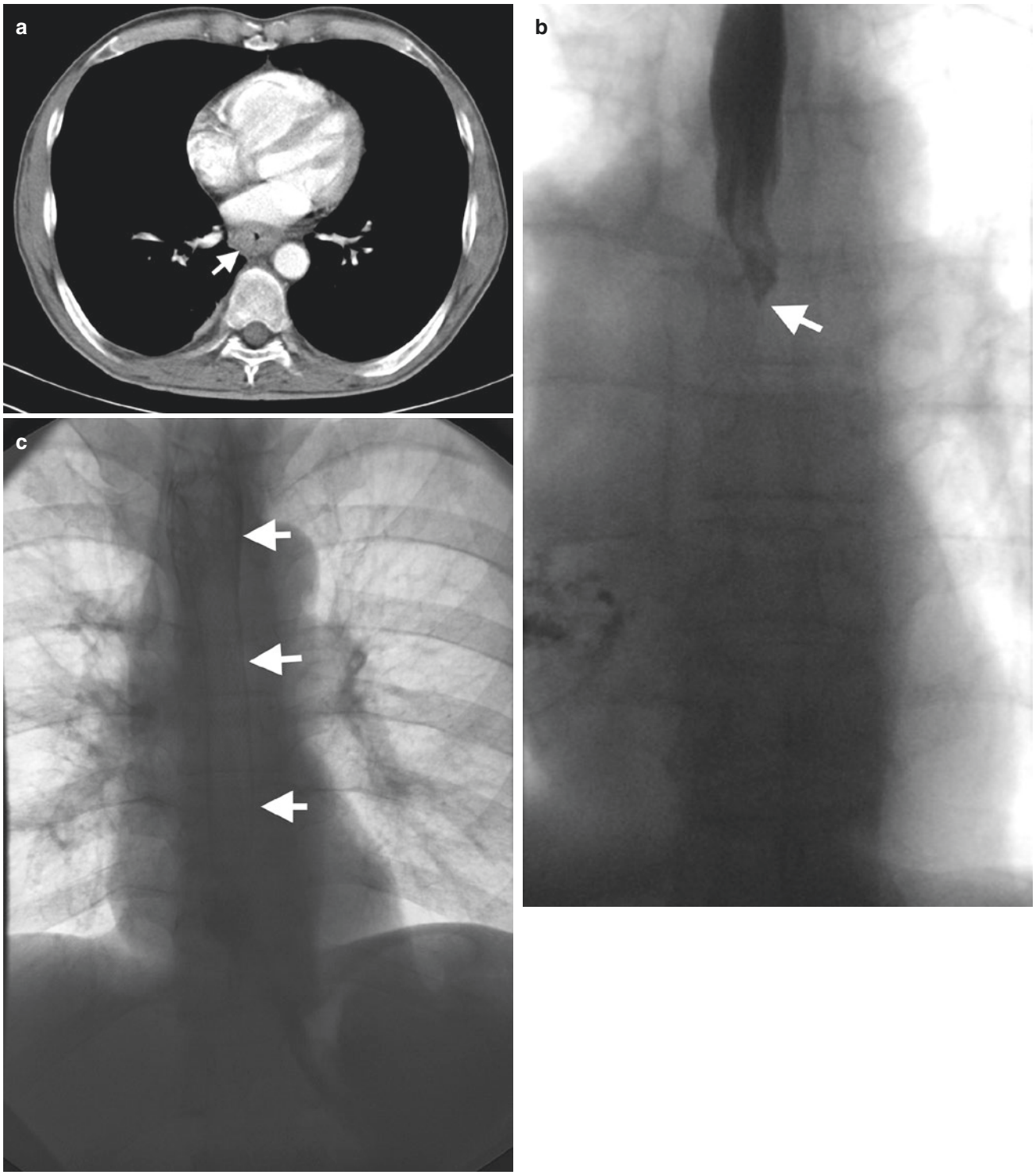


Fig. 31.11 Esophageal stent placement in a 50-year-old male patient who was deemed inoperable based on extensive intra-abdominal metastatic disease. (**a**) Axial contrast-enhanced computed tomography (CT) image demonstrates circumferential wall thickening (arrow) in the thoracic esophagus. (**b**) Fluoroscopy image revealed the almost complete blockage of barium passage (arrow) at the tumor location. (**c**) Post-deployment fluoroscopy view revealed successful coverage of the stenotic esophageal segment with the stent (arrows)

this is not an issue in patients with biodegradable stents as they resolve spontaneously after a certain period of time.

The technical success rate is extremely high (>95%) in cancers of thoracic and abdominal esophagus, with a reported mortality rate of 0.5–2% [117]. As for the cervical portion of the esophagus, special stents have been designed. These stents have lower radial expansion force, with a small proximal collar to reduce reflux, or with a proximal delivery system to secure correct positioning [121, 122]. Orotracheal compression has been reported in patients having stents located above the carinal level [123].

Gastroduodenal Stenting

Stenting can be a very helpful palliation alternative for maintaining gastroduodenal patency where curative surgery is not a viable alternative [124] (Fig. 31.12a, b). Duodenal obstruction due to advanced stage pancreatic cancer is the most common indication for gastroduodenal stenting (GDS). As its onset of action is quick and placement causes minimal morbidity, GDS is an excellent alternative to palliative surgery in patients with poor life expectancy [125, 126]. In a prospective randomized trial comparing laparoscopic gastrojejunostomy with duodenal stenting, stenting was found to be superior to surgery for relieving gastric outflow obstruction in terms of morbidity, postoperative pain, hospital stay, and 1-month quality of life [127]. The clinical success parameters for GDS are relief of obstruction, improvement in nutritional status and oral feeding, and a better quality of life. As for GDS the success rate is high and was reported to be between 79% and 91% [128, 129].

The procedure is safe with a morbidity between 11% and 43% [130]. Bleeding, perforation, biliary obstruction (in patients treated with covered stents), and migration are among the early complications [131]. Stent migration, perforation, duodenal fistula, and stent fracture should be considered as delayed complications. Previous dilatation, technically difficult stent placement or the use of rigid guidewires, concomitant corticosteroid use, and chemotherapy should be counted among the risk factors for perforation.

Colonic Stenting

Acute colonic obstruction is the presenting symptom in a significant portion of colorectal cancers and immediate surgery in these patients carries high morbidity (40–60%) and mortality (8–20%) [132, 133]. Colonic stenting has emerged since the 1990s first as a palliative procedure and then as a bridge to

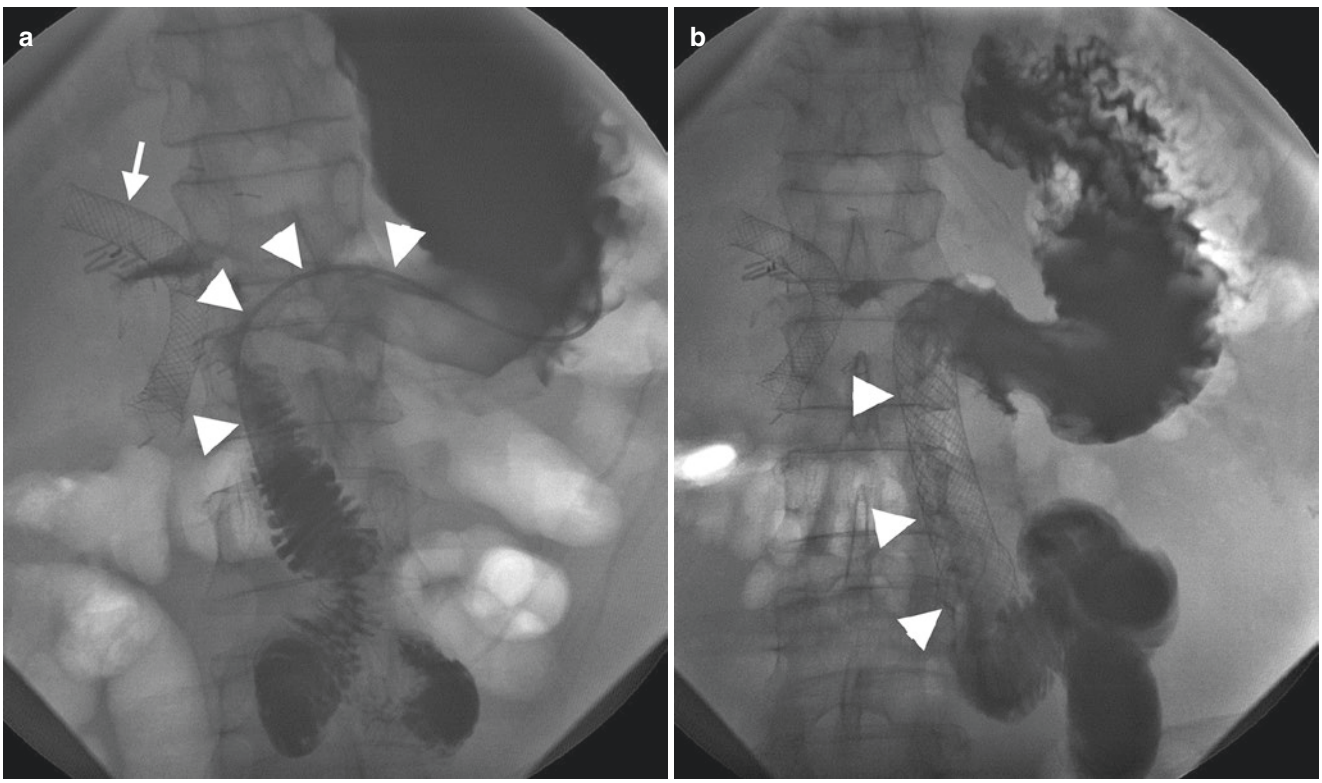


Fig. 31.12 A 65-year-old female patient with known inoperable pancreatic cancer who previously underwent palliative gastrojejunostomy for gastric outlet obstruction. She now presented with recurrent symptoms. (**a**) Fluoroscopy image demonstrates long-segment tight stenosis at the anastomosis (arrowheads). Also note the previously placed biliary stent (arrow). (**b**) Post-deployment fluoroscopy image demonstrates well-expanded stent (arrowheads) covering the stenosed lumen

permanent surgery to achieve better clinical outcomes in these patients [134]. The technical success rate is reported to be high (90%). However, it should be noted that inability to cross the stricture with the guidewire, difficult anatomy with extensive tortuosity of the involved bowel segment, increased enteral peristalsis, or tight stenoses are limiting factors for the technical success of the procedure [134–137].

Percutaneous Gastrostomy

Gastrostomy is a commonly performed interventional radiology procedure in patients with swallowing difficulties, especially in patients with head and neck cancer and neurological disorders (Fig. 31.13a–c). Malnutrition is a significant clinical problem in these patients with studies showing 29–33%

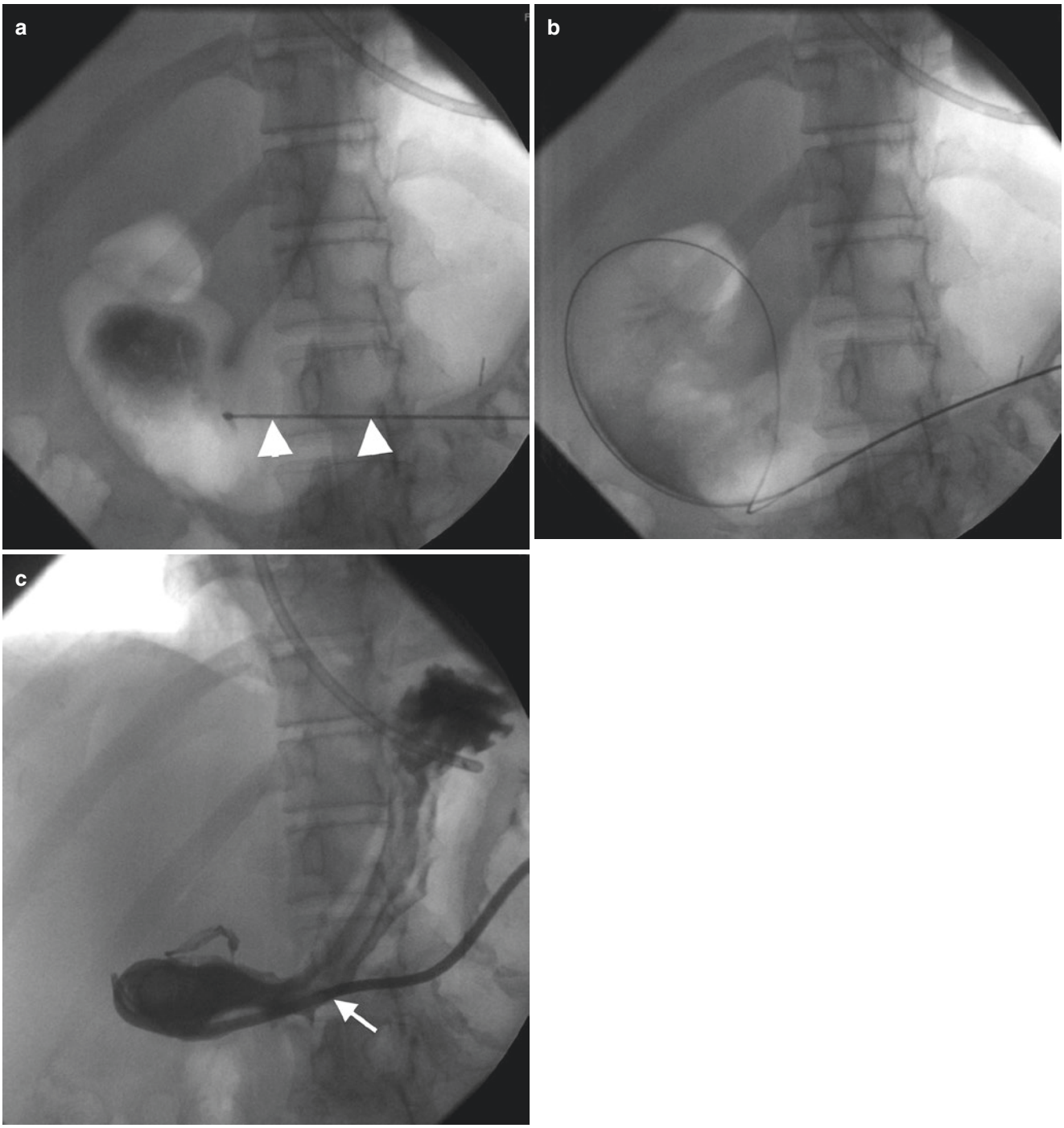


Fig. 31.13 A 35-year-old male patient with newly diagnosed locally invasive hypopharyngeal tumor referred for gastrostomy placement due to significantly limited oral intake. (**a**) Fluoroscopy image demonstrates successful puncture of the distended stomach with the hollow needle (arrowheads). (**b**) Fluoroscopy image shows successful advancement of the guidewire through the hollow needle. (**c**) Final image reveals successful placement of the gastrostomy tube (arrow)

of inpatients are malnourished [138]. Aside from basic hydration and nutrition, enteral feeding is especially important in patients with metabolic stress [139].

Surgical gastrostomy is a well-established procedure that has been performed since the nineteenth century. The first fully percutaneous gastrostomy was reported in the early 1980s [140], and since then it has been widely used.

There are very few absolute contraindications for percutaneous gastrostomy placement (PGP) including severe uncorrected coagulopathy, bowel ischemia, active peritonitis, and GI obstruction (unless the aim of the procedure is palliative rather than nutrition). Ascites, severe portal hypertension with varices, postsurgery stomach, the presence of ventriculoperitoneal shunt, and long-term immunosuppression should be considered among relative contraindications for PGP [141].

The technical success of PGP is high with reported rates of 95–100% [142–144]. Rates of complication have been reported to be lower in patients with radiologically inserted gastrostomy compared to endoscopically placed gastrostomy [145, 146].

Bleeding, peritonitis, and colonic perforation should be considered among the major complications related to the procedure, but these complications may be significantly decreased with a meticulous technique.

Celiac Neurolysis

Abdominal pain is a common problem in patients with abdominal cancers and can sometimes be debilitating for the affected patients. The management of this issue is complex and may often necessitate the use of high-dose narcotics with subsequent potential side effects [147].

Anatomically, the pain fibers in the upper abdomen relay through the splanchnic nerves and the celiac plexus. Celiac plexus refers to the collection of nerve fibers located in the retroperitoneum along the anterolateral wall of the abdominal aorta [148]. The celiac plexus supplies sensory afferent fibers to several organs in the upper abdomen including: liver, biliary system, pancreas, spleen, adrenal glands, kidneys, mesentery, and stomach and bowel segments. With this anatomic information, it is not surprising to consider blocking the nociceptive receptors in the celiac plexus might be a viable option in the alleviation of intractable abdominal pain in patients with cancers of the aforementioned organs. Anatomically, the celiac plexus is located in the retroperitoneal space and embedded in the fat tissue, located just anterior to the abdominal aorta, caudad to the level of the origin of the celiac artery [147].

Ethanol and phenol are the most commonly used agents for this purpose, and the procedure may be performed under fluoroscopy, ultrasonography, and CT [149] (Fig. 31.14a, b).

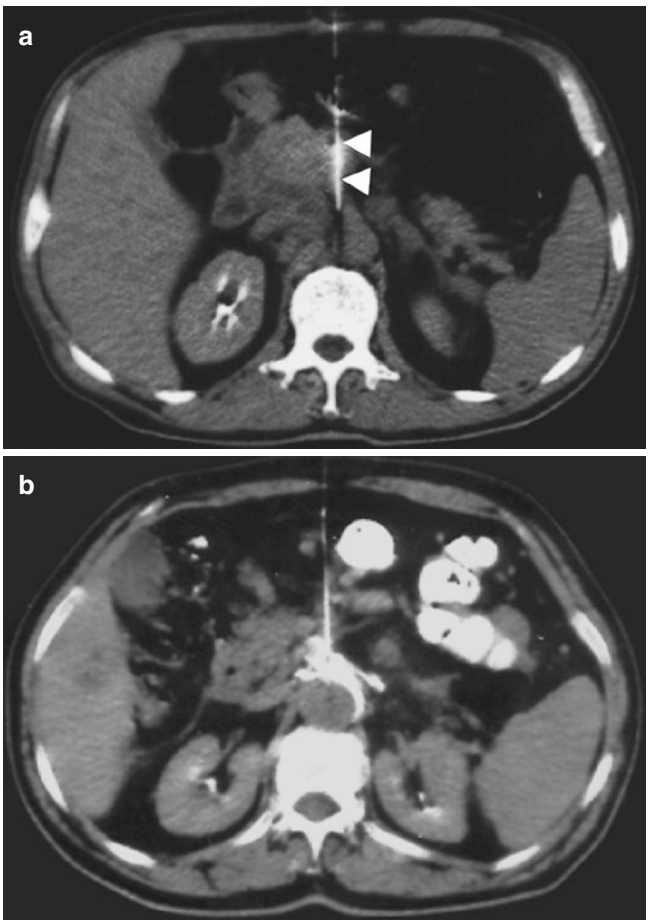


Fig. 31.14 A 45-year-old male patient presenting with intractable abdominal pain, unresponsive to full-dose narcotics, due to local invasive inoperable pancreatic adenocancer. (**a**) Axial computed tomography (CT) image demonstrates successful location of the hollow needle (arrowheads) right anterior to the abdominal aorta. (**b**) Axial CT image shows confirmation of the correct location of the needle after injection of contrast through the hollow needle. After confirming the correct location, absolute alcohol was injected to this location (not shown). Patient almost fully responded to the procedure with minimal narcotic support

Celiac neurolysis is a safe procedure with a reported complication rate of less than 2% [150, 151]. Orthostatic hypotension, back pain, and transient diarrhea are common after the procedure [152]. Bed rest for 12 hours after the procedure and adequate hydration are helpful measures to counter the effects of autonomic dysfunction that emerges after the procedure [147]. Other severe side effects are rare.

Celiac neurolysis is a highly effective procedure with a long-lasting benefit in 70–90% of patients with various upper abdominal cancers [150]. The procedure is particularly effective in patients with pancreatic cancer. The pain may be completely abolished with celiac neurolysis alone in 10–24% of the patients and in 80–90% of the patients when combined with other treatment methods [153, 154].

Conclusion

Interventional oncology has recently emerged as one of the key players in the management of oncology patients. In today's modern oncology practice, the interventional radiologists, especially the ones experienced in the treatment of cancer patients, play an indispensable role in the clinical management and follow-up. Interventional radiologists are one of the permanent members of tumor boards, and they provide significant support to their surgical and medical oncologist colleagues. It will be of no surprise that, with their constant intellectual efforts and subsequent creativity, they will play even more important roles in the near future.

References

1. Rosch J, Keller FS, Kaufman JA. The birth, early years, and future of interventional radiology. J Vasc Interv Radiol. 2003;14(7):841–53.
2. Charboneau JW, Reading CC, Welch TJ. CT and sonographically guided needle biopsy: current techniques and new innovations. AJR Am J Roentgenol. 1990;154(1):1–10.
3. Reading CC, Charboneau JW, James EM, Hurt MR. Sonographically guided percutaneous biopsy of small (3 cm or less) masses. AJR Am J Roentgenol. 1988;151(1): 189–92.
4. Odisio BC, Wallace MJ. Image-guided interventions in oncology. Surg Oncol Clin N Am. 2014;23(4):937–55.
5. Hopper KD, Abendroth CS, Sturtz KW, Matthews YL, Shirk SJ, Stevens LA. Blinded comparison of biopsy needles and automated devices in vitro: 2. Biopsy of medical renal disease. AJR Am J Roentgenol. 1993;161(6):1299–301.
6. Hopper KD, Abendroth CS, Sturtz KW, Matthews YL, Shirk SJ, Stevens LA. Blinded comparison of biopsy needles and automated devices in vitro: 1. Biopsy of diffuse hepatic disease. AJR Am J Roentgenol. 1993;161(6):1293–7.
7. Gupta S, Wallace MJ, Cardella JF, Kundu S, Miller DL, Rose SC, et al. Quality improvement guidelines for percutaneous needle biopsy. J Vasc Interv Radiol. 2010;21(7):969–75.
8. Kim KW, Kim MJ, Kim HC, Park SH, Kim SY, Park MS, et al. Value of "patent track" sign on Doppler sonography after percutaneous liver biopsy in detection of postbiopsy bleeding: a prospective study in 352 patients. AJR Am J Roentgenol. 2007;189(1):109–16.
9. Geraghty PR, Kee ST, McFarlane G, Razavi MK, Sze DY, Dake MD. CT-guided transthoracic needle aspiration biopsy of pulmonary nodules: needle size and pneumothorax rate. Radiology. 2003;229(2):475–81.
10. Schubert P, Wright CA, Louw M, Brundyn K, Theron J, Bolliger CT, et al. Ultrasound-assisted transthoracic biopsy: cells or sections? Diagn Cytopathol. 2005;33(4):233–7.
11. Nordback IH, Pitt HA, Coleman J, Venbrux AC, Dooley WC, Yeu NN, et al. Unresectable hilar cholangiocarcinoma: percutaneous versus operative palliation. Surgery. 1994;115(5):597–603.
12. Ozden I, Tekant Y, Bilge O, Acarli K, Alper A, Emre A, et al. Endoscopic and radiologic interventions as the leading causes of severe cholangitis in a tertiary referral center. Am J Surg. 2005;189(6):702–6.
13. Sutter CM, Ryu RK. Percutaneous management of malignant biliary obstruction. Tech Vasc Interv Radiol. 2015;18(4):218–26.
14. Saad WE, Wallace MJ, Wojak JC, Kundu S, Cardella JF. Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and percutaneous cholecystostomy. J Vasc Interv Radiol. 2010;21(6):789–95.
15. Garcia MJ, Epstein DS, Dignazio MA. Percutaneous approach to the diagnosis and treatment of biliary tract malignancies. Surg Oncol Clin N Am. 2009;18(2):241–56, viii.
16. Madoff DC, Wallace MJ. Palliative treatment of unresectable bile duct cancer: which stent? Which approach? Surg Oncol Clin N Am. 2002;11(4):923–39.
17. Lee BH, Choe DH, Lee JH, Kim KH, Chin SY. Metallic stents in malignant biliary obstruction: prospective long-term clinical results. AJR Am J Roentgenol. 1997;168(3):741–5.
18. Wagner HJ, Knyrim K, Vakil N, Klose KJ. Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial. Endoscopy. 1993;25(3):213–8.
19. Farrell TA, Hicks ME. A review of radiologically guided percutaneous nephrostomies in 303 patients. J Vasc Interv Radiol. 1997;8(5):769–74.
20. Ramchandani P, Cardella JF, Grassi CJ, Roberts AC, Sacks D, Schwartzberg MS, et al. Quality improvement guidelines for percutaneous nephrostomy. J Vasc Interv Radiol. 2003;14(9 Pt 2):S277–81.
21. Klahr S. Pathophysiology of obstructive nephropathy. Kidney Int. 1983;23(2):414–26.
22. Vaughan ED Jr, Marion D, Poppas DP, Felsen D. Pathophysiology of unilateral ureteral obstruction: studies from Charlottesville to New York. J Urol. 2004;172(6 Pt 2):2563–9.
23. Dagli M, Ramchandani P. Percutaneous nephrostomy: technical aspects and indications. Semin Interv Radiol. 2011;28(4):424–37.
24. Zagoria RJ, Dyer RB. Do's and don't's of percutaneous nephrostomy. Acad Radiol. 1999;6(6):370–7.
25. Ahrar K, Matin S, Wood CG, Wallace MJ, Gupta S, Madoff DC, et al. Percutaneous radiofrequency ablation of renal tumors: technique, complications, and outcomes. J Vasc Interv Radiol. 2005;16(5):679–88.
26. Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatology. 2010;51(4):1284–90.
27. Gillams AR, Lees WR. Five-year survival following radiofrequency ablation of small, solitary, hepatic colorectal metastases. J Vasc Interv Radiol. 2008;19(5):712–7.
28. Gillams AR, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol. 2009;19(5):1206–13.
29. Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg. 2003;90(10):1240–3.
30. Simon CJ, Dupuy DE, Mayo-Smith WW. Microwave ablation: principles and applications. Radiographics. 2005;25(Suppl 1):S69–83.
31. Lubner MG, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. J Vasc Interv Radiol. 2010;21(8 Suppl):S192–203.
32. Saldanha DF, Khiatani VL, Carrillo TC, Yap FY, Bui JT, Knuttinen MG, et al. Current tumor ablation technologies: basic science and device review. Semin Interv Radiol. 2010;27(3):247–54.
33. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. Ann Surg Oncol. 2010;17(1):171–8.
34. Wright AS, Sampson LA, Warner TF, Mahvi DM, Lee FT Jr. Radiofrequency versus microwave ablation in a hepatic porcine model. Radiology. 2005;236(1):132–9.
35. Georgiades CS, Hong K, Bizzell C, Geschwind JF, Rodriguez R. Safety and efficacy of CT-guided percutaneous cryoablation for renal cell carcinoma. J Vasc Interv Radiol. 2008;19(9):1302–10.

36. Shock SA, Laeseke PF, Sampson LA, Lewis WD, Winter TC 3rd, Fine JP, et al. Hepatic hemorrhage caused by percutaneous tumor ablation: radiofrequency ablation versus cryoablation in a porcine model. Radiology. 2005;236(1):125–31.
37. Coster HG. A quantitative analysis of the voltage-current relationships of fixed charge membranes and the associated property of "punch-through". Biophys J. 1965;5(5):669–86.
38. Davalos RV, Mir IL, Rubinsky B. Tissue ablation with irreversible electroporation. Ann Biomed Eng. 2005;33(2):223–31.
39. Silk M, Tahour D, Srimathveeravalli G, Solomon SB, Thornton RH. The state of irreversible electroporation in interventional oncology. Semin Interv Radiol. 2014;31(2):111–7.
40. Charpentier KP, Wolf F, Noble L, Winn B, Resnick M, Dupuy DE. Irreversible electroporation of the liver and liver hilum in swine. HPB (Oxford). 2011;13(3):168–73.
41. Schoellnast H, Monette S, Ezell PC, Deodhar A, Maybody M, Erinjeri JP, et al. Acute and subacute effects of irreversible electroporation on nerves: experimental study in a pig model. Radiology. 2011;260(2):421–7.
42. Schoellnast H, Monette S, Ezell PC, Maybody M, Erinjeri JP, Stubblefield MD, et al. The delayed effects of irreversible electroporation ablation on nerves. Eur Radiol. 2013;23(2):375–80.
43. Silk MT, Wimmer T, Lee KS, Srimathveeravalli G, Brown KT, Kingham PT, et al. Percutaneous ablation of peribiliary tumors with irreversible electroporation. J Vasc Interv Radiol. 2014;25(1):112–8.
44. Ziemlewicz TJ, Wells SA, Lubner MG, Brace CL, Lee FT Jr, Hinshaw JL. Hepatic tumor ablation. Surg Clin North Am. 2016;96(2):315–39.
45. Patel SR, Hinshaw JL, Lubner MG, Lee FT Jr, Nakada SY, Hedican SP. Hydrodissection using an iodinated contrast medium during percutaneous renal cryoablation. J Endourol. 2012;26(5):463–6.
46. Yu H, Burke CT. Comparison of percutaneous ablation technologies in the treatment of malignant liver tumors. Semin Interv Radiol. 2014;31(2):129–37.
47. de Meijer VE, Kalish BT, Puder M, Ijzermans JN. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. Br J Surg. 2010;97(9):1331–9.
48. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg. 2007;94(11):1386–94.
49. Shoup M, Gonen M, D'Angelica M, Jarnagin WR, DeMatteo RP, Schwartz LH, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg. 2003;7(3):325–30.
50. Brouquet A, Andreou A, Shindoh J, Vauthey JN. Methods to improve resectability of hepatocellular carcinoma. Recent Results Cancer Res. 2013;190:57–67.
51. Rees M, John TG. Current status of surgery in colorectal metastases to the liver. Hepato-Gastroenterology. 2001;48(38):341–4.
52. Anaya DA, Blazer DG, Abdalla EK. Strategies for resection using portal vein embolization: hepatocellular carcinoma and hilar cholangiocarcinoma. Semin Interv Radiol. 2008;25(2):110–22.
53. Vauthey JN, Dixon E, Abdalla EK, Helton WS, Pawlik TM, Taouli B, et al. Pretreatment assessment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford). 2010;12(5):289–99.
54. Orcutt ST, Kobayashi K, Sultenfuss M, Hailey BS, Sparks A, Satpathy B, et al. Portal vein embolization as an oncosurgical strategy prior to major hepatic resection: anatomic, surgical, and technical considerations. Front Surg. 2016;3:14.
55. van Lienden KP, van den Esschert JW, de Graaf W, Bipat S, Lameris JS, van Gulik TM, et al. Portal vein embolization before liver resection: a systematic review. Cardiovasc Intervent Radiol. 2013;36(1):25–34.
56. Hong K, Khwaja A, Liapi E, Torbenson MS, Georgiades CS, Geschwind JF. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res. 2006;12(8):2563–7.
57. Chapiro J, Tacher V, Geschwind JF. Intraarterial therapies for primary liver cancer: state of the art. Expert Rev Anticancer Ther. 2013;13(10):1157–67.
58. Constantin M, Fundueanu G, Bortolotti F, Cortesi R, Ascenzi P, Menegatti E. Preparation and characterisation of poly(vinyl alcohol)/cyclodextrin microspheres as matrix for inclusion and separation of drugs. Int J Pharm. 2004;285(1–2):87–96.
59. Qian J, Truebenbach J, Graepler F, Pereira P, Huppert P, Eul T, et al. Application of poly-lactide-co-glycolide-microspheres in the transarterial chemoembolization in an animal model of hepatocellular carcinoma. World J Gastroenterol. 2003;9(1):94–8.
60. Lewis AL, Gonzalez MV, Lloyd AW, Hall B, Tang Y, Willis SL, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol. 2006;17(2 Pt 1):335–42.
61. Gonzalez MV, Tang Y, Phillips GJ, Lloyd AW, Hall B, Stratford PW, et al. Doxorubicin eluting beads-2: methods for evaluating drug elution and in-vitro: in-vivo correlation. J Mater Sci Mater Med. 2008;19(2):767–75.
62. Ahmadzadehfar H, Sabet A, Biermann K, Muckle M, Brockmann H, Kuhl C, et al. The significance of 99mTc-MAA SPECT/CT liver perfusion imaging in treatment planning for 90Y-microsphere selective internal radiation treatment. J Nucl Med. 2010;51(8):1206–12.
63. Lewandowski RJ, Geschwind JF, Liapi E, Salem R. Transcatheter intraarterial therapies: rationale and overview. Radiology. 2011;259(3):641–57.
64. Pellerin O, Geschwind JF. Intra-arterial treatment of liver metastases from colorectal carcinoma. J Radiol. 2011;92(9):835–41.
65. Minocha J, Salem R, Lewandowski RJ. Transarterial chemoembolization and yittrium-90 for liver cancer and other lesions. Clin Liver Dis. 2014;18(4):877–90.
66. Bhutiani N, Martin RC 2nd. Transarterial therapy for colorectal liver metastases. Surg Clin North Am. 2016;96(2):369–91.
67. Gaur SK, Friese JL, Sadow CA, Ayyagari R, Binkert CA, Schenker MP, et al. Hepatic arterial chemoembolization using drug-eluting beads in gastrointestinal neuroendocrine tumor metastatic to the liver. Cardiovasc Intervent Radiol. 2011;34(3):566–72.
68. Liapi E, Geschwind JF, Vossen JA, Buijs M, Georgiades CS, Bluemke DA, et al. Functional MRI evaluation of tumor response in patients with neuroendocrine hepatic metastasis treated with transcatheter arterial chemoembolization. AJR Am J Roentgenol. 2008;190(1):67–73.
69. Memon K, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Sato KT, et al. Radioembolization for neuroendocrine liver metastases: safety, imaging, and long-term outcomes. Int J Radiat Oncol Biol Phys. 2012;83(3):887–94.
70. Rhee TK, Lewandowski RJ, Liu DM, Mulcahy MF, Takahashi G, Hansen PD, et al. 90Y radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. Ann Surg. 2008;247(6):1029–35.
71. Roche A, Girish BV, de Baere T, Baudin E, Boige V, Elias D, et al. Trans-catheter arterial chemoembolization as first-line treatment for hepatic metastases from endocrine tumors. Eur Radiol. 2003;13(1):136–40.
72. Cartier V, Aube C. Diagnosis of hepatocellular carcinoma. Diagn Interv Imaging. 2014;95(7–8):709–19.
73. Doyon DMA, Jourde AN, Regensberg C, Frileux C. L'embolisation artérielle hépatique dans les tumeurs malignesdu liver. Ann Radiol. 1974;17:593–603.
74. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Transarterial therapy for hepatocellular carcinoma:

which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol. [Meta-Analysis Review]. 2007;30(1):6–25.
75. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2008;100(10):698–711.
76. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. [Practice Guideline]. 2011;53(3):1020–2.
77. Anonymous. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. [Practice Guideline]. 2012;56(4):908–43.
78. Boulin M, Delhom E, Pierredon-Foulongne MA, Cercueil JP, Guiu B. Transarterial chemoembolization for hepatocellular carcinoma: an old method, now flavor of the day. Diagn Interv Imaging. 2015;96(6):607–15.
79. Raoul JL, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev. [Research Support, Non-U.S. Gov't Review]. 2011;37(3):212–20.
80. Lencioni R. Management of hepatocellular carcinoma with transarterial chemoembolization in the era of systemic targeted therapy. Crit Rev Oncol Hematol. [Review]. 2012;83(2):216–24.
81. Cao DD, Xu HL, Liu L, Zheng YF, Gao SF, Xu XM, et al. Thalidomide combined with transcatheter arterial chemoembolization for primary hepatocellular carcinoma: a systematic review and meta-analysis. Oncotarget. [Meta-Analysis Review]. 2017;8(27):44976–93.
82. Lencioni R, Petruzzi P, Crocetti L. Chemoembolization of hepatocellular carcinoma. Semin Interv Radiol. [Review]. 2013;30(1):3–11.
83. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Interv Radiol. [Clinical Trial, Phase II Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2010;33(1):41–52.
84. Sun Z, Li G, Ai X, Luo B, Wen Y, Zhao Z, et al. Hepatic and biliary damage after transarterial chemoembolization for malignant hepatic tumors: incidence, diagnosis, treatment, outcome and mechanism. Crit Rev Oncol Hematol. [Research Support, Non-U.S. Gov't Review]. 2011;79(2):164–74.
85. Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer. [Comparative Study Evaluation Studies Research Support, Non-U.S. Gov't]. 2009;115(3):616–23.
86. Gillmore R, Stuart S, Kirkwood A, Hameeduddin A, Woodward N, Burroughs AK, et al. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol. [Research Support, Non-U.S. Gov't]. 2011;55(6):1309–16.
87. Shim JH, Lee HC, Kim SO, Shin YM, Kim KM, Lim YS, et al. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology. [Comparative Study Validation Studies]. 2012;262(2):708–18.
88. Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis. [Research Support, Non-U.S. Gov't Review]. 2012;32(4):348–59.
89. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33(1):41–52.
90. Vogl TJ, Lammer J, Lencioni R, Malagari K, Watkinson A, Pilleul F, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. AJR Am J Roentgenol. [Multicenter Study Randomized Controlled Trial]. 2011;197(4):W562–70.
91. Deschamps F, Solomon SB, Thornton RH, Rao P, Hakime A, Kuoch V, et al. Computed analysis of three-dimensional cone-beam computed tomography angiography for determination of tumor-feeding vessels during chemoembolization of liver tumor: a pilot study. Cardiovasc Intervent Radiol. 2010;33(6):1235–42.
92. Nicolini A, Martinetti L, Crespi S, Maggioni M, Sangiovanni A. Transarterial chemoembolization with epirubicin-eluting beads versus transarterial embolization before liver transplantation for hepatocellular carcinoma. J Vasc Interv Radiol: JVIR. [Comparative Study]. 2010;21(3):327–32.
93. Geschwind JF, Kudo M, Marrero JA, Venook AP, Chen XP, Bronowicki JP, et al. TACE treatment in patients with sorafenib-treated unresectable hepatocellular carcinoma in clinical practice: final analysis of GIDEON. Radiology. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2016;279(2):630–40.
94. Lewis AL, Taylor RR, Hall B, Gonzalez MV, Willis SL, Stratford PW. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol: JVIR: JVIR. 2006;17(8):1335–43.
95. Poon RT, Tso WK, Pang RW, Ng KK, Woo R, Tai KS, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol. [Clinical Trial, Phase I Clinical Trial, Phase II Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2007;5(9):1100–8.
96. Nishikawa H, Kita R, Kimura T, Osaki Y. Transcatheter arterial embolic therapies for hepatocellular carcinoma: a literature review. Anticancer Res. [Review]. 2014;34(12):6877–86.
97. Spreafico C, Cascella T, Facciorusso A, Sposito C, Rodolfo L, Morosi C, et al. Transarterial chemoembolization for hepatocellular carcinoma with a new generation of beads: clinical-radiological outcomes and safety profile. Cardiovasc Intervent Radiol. 2015;38(1):129–34.
98. Dinca HPJ, Baylatry MT, Ghegediban SH, Pascale F, Manfait M, editors. Why do small size doxorubicin-eluting microspheres induce more tissue necrosis than larger ones? A comparative study in healthy pig liver (oral communication 2206-2). CIRSE annual meeting; 2012; Lisbon.
99. Malagari K, Pomoni M, Moschouris H, Kelekis A, Charokopakis A, Bouma E, et al. Chemoembolization of hepatocellular carcinoma with hepasphere 30–60 μm. Safety and efficacy study. Cardiovasc Intervent Radiol. 2014;37(1):165–75.
100. Leung DA, Goin JE, Sickles C, Raskay BJ, Soulen MC. Determinants of postembolization syndrome after hepatic chemoembolization. J Vasc Interv Radiol. 2001;12(3):321–6.
101. Geschwind JF, Salem R, Carr BI, Soulen MC, Thurston KG, Goin KA, et al. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. Gastroenterology. 2004;127(5 Suppl 1):S194–205.
102. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. Am J Roentgenol Radium Therapy, Nucl Med. 1965;93:200–8.
103. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys. 1995;31(5):1237–48.

104. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodologic considerations. J Vasc Interv Radiol. 2006;17(8):1251–78.
105. Virdee PS, Moschandreas J, Gebski V, Love SB, Francis EA, Wasan HS, et al. Protocol for combined analysis of FOXFIRE, SIRFLOX, and FOXFIRE-global randomized phase III trials of chemotherapy +/− selective internal radiation therapy as first-line treatment for patients with metastatic colorectal cancer. JMIR Res Protoc. 2017;6(3):e43.
106. van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol. [Clinical Trial, Phase III Comparative Study Randomized Controlled Trial]. 2016;34(15):1723–31.
107. Riaz A, Awais R, Salem R. Side effects of yttrium-90 radioembolization. Front Oncol. 2014;4:198.
108. Piedbois P, Buyse M, Kemeny N, Rougier P, Carlson R, Allen-Mersh T, et al. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Natl Cancer Inst. [Meta-Analysis Research Support, Non--U.S. Gov't]. 1996;88(5):252–8.
109. Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol. [Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural]. 2006;24(9):1395–403.
110. Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. Lancet. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 1994;344(8932):1255–60.
111. Kennedy A. Radioembolization of hepatic tumors. J Gastrointest Oncol. [Review]. 2014;5(3):178–89.
112. Committee AT, Varadarajulu S, Banerjee S, Barth B, Desilets D, Kaul V, et al. Enteral stents. Gastrointest Endosc. 2011;74(3):455–64.
113. Dai YX, Li CY, Xie Y, Liu XD, Zhang JX, Zhou J, et al. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev. 2014;(10).
114. Katsanos K, Sabharwal T, Adam A. Stenting of the lower gastrointestinal tract: current status. Cardiovasc Intervent Radiol. 2011;34(3):462–73.
115. Bergquist H, Johnsson E, Nyman J, Rylander H, Hammerlid E, Friesland S, et al. Combined stent insertion and single high-dose brachytherapy in patients with advanced esophageal cancer--results of a prospective safety study. Dis Esophagus. 2012;25(5):410–5.
116. Vakil N, Morris AI, Marcon N, Segalin A, Peracchia A, Bethge N, et al. A prospective, randomized, controlled trial of covered expandable metal stents in the palliation of malignant esophageal obstruction at the gastroesophageal junction. Am J Gastroenterol. 2001;96(6):1791–6.
117. Malgras B, Lo Dico R, Pautrat K, Dohan A, Boudiaf M, Pocard M, et al. Gastrointestinal stenting: current status and imaging features. Diagn Interv Imaging. 2015;96(6):593–606.
118. Shin JH, Song HY, Kim JH, Kim SB, Lee GH, Park SI, et al. Comparison of temporary and permanent stent placement with concurrent radiation therapy in patients with esophageal carcinoma. J Vasc Interv Radiol. 2005;16(1):67–74.
119. Song HY, Lee DH, Seo TS, Kim SB, Jung HY, Kim JH, et al. Retrievable covered nitinol stents: experiences in 108 patients with malignant esophageal strictures. J Vasc Interv Radiol. 2002;13(3):285–93.
120. Stivaros SM, Williams LR, Senger C, Wilbraham L, Laasch HU. Woven polydioxanone biodegradable stents: a new treatment option for benign and malignant oesophageal strictures. Eur Radiol. 2010;20(5):1069–72.
121. Shim CS, Jung IS, Bhandari S, Ryu CB, Hong SJ, Kim JO, et al. Management of malignant strictures of the cervical esophagus with a newly-designed self-expanding metal stent. Endoscopy. 2004;36(6):554–7.
122. Siersema PD. Esophageal cancer. Gastroenterol Clin N Am. 2008;37(4):943–64, x.
123. Libby ED, Fawaz R, Leano AM, Hassoun PM. Airway complication of expandable stents. Gastrointest Endosc. 1999;49(1):136–7.
124. Dormann A, Meisner S, Verin N, Lang AW. Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness. Endoscopy. 2004;36(6):543–50.
125. Fiori E, Lamazza A, De Cesare A, Bononi M, Volpino P, Schillaci A, et al. Palliative management of malignant rectosigmoidal obstruction. Colostomy vs. endoscopic stenting. A randomized prospective trial. Anticancer Res. 2004;24(1):265–8.
126. Jeurnink SM, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc. 2010;71(3):490–9.
127. Mehta S, Hindmarsh A, Cheong E, Cockburn J, Saada J, Tighe R, et al. Prospective randomized trial of laparoscopic gastrojejunostomy versus duodenal stenting for malignant gastric outflow obstruction. Surg Endosc. 2006;20(2):239–42.
128. Del Piano M, Ballare M, Montino F, Todesco A, Orsello M, Magnani C, et al. Endoscopy or surgery for malignant GI outlet obstruction? Gastrointest Endosc. 2005;61(3):421–6.
129. van Hooft JE, Uitdehaag MJ, Bruno MJ, Timmer R, Siersema PD, Dijkgraaf MG, et al. Efficacy and safety of the new wallflex enteral stent in palliative treatment of malignant gastric outlet obstruction (DUOFLEX study): a prospective multicenter study. Gastrointest Endosc. 2009;69(6):1059–66.
130. Masci E, Viale E, Mangiavillano B, Contin G, Lomazzi A, Buffoli F, et al. Enteral self-expandable metal stent for malignant luminal obstruction of the upper and lower gastrointestinal tract: a prospective multicentric study. J Clin Gastroenterol. 2008;42(4):389–94.
131. Nassif T, Prat F, Meduri B, Fritsch J, Choury AD, Dumont JL, et al. Endoscopic palliation of malignant gastric outlet obstruction using self-expandable metallic stents: results of a multicenter study. Endoscopy. 2003;35(6):483–9.
132. Pearce NW, Scott SD, Karran SJ. Timing and method of reversal of Hartmann's procedure. Br J Surg. 1992;79(8):839–41.
133. Tan CJ, Dasari BV, Gardiner K. Systematic review and meta-analysis of randomized clinical trials of self-expanding metallic stents as a bridge to surgery versus emergency surgery for malignant left-sided large bowel obstruction. Br J Surg. 2012;99(4):469–76.
134. Tejero E, Mainar A, Fernandez L, Tobio R, De Gregorio MA. New procedure for the treatment of colorectal neoplastic obstructions. Dis Colon Rectum. 1994;37(11):1158–9.
135. Aitken DG, Horgan AF. Endoluminal insertion of colonic stents. Surg Oncol. 2007;16(1):59–63.
136. Tilney HS, Lovegrove RE, Purkayastha S, Sains PS, Weston-Petrides GK, Darzi AW, et al. Comparison of colonic stenting and open surgery for malignant large bowel obstruction. Surg Endosc. 2007;21(2):225–33.
137. Watt AM, Faragher IG, Griffin TT, Rieger NA, Maddern GJ. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. Ann Surg. 2007;246(1):24–30.

138. Vanderwee K, Clays E, Bocquaert I, Gobert M, Folens B, Defloor T. Malnutrition and associated factors in elderly hospital patients: a Belgian cross-sectional, multi-centre study. Clin Nutr. 2010;29(4):469–76.
139. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–316.
140. Preshaw RM. A percutaneous method for inserting a feeding gastrostomy tube. Surg Gynecol Obstet. 1981;152(5):658–60.
141. Sutcliffe J, Wigham A, McEniff N, Dvorak P, Crocetti L, Uberoi R. CIRSE standards of practice guidelines on gastrostomy. Cardiovasc Intervent Radiol. 2016;39(7):973–87.
142. de Baere T, Chapot R, Kuoch V, Chevallier P, Delille JP, Domenge C, et al. Percutaneous gastrostomy with fluoroscopic guidance: single-center experience in 500 consecutive cancer patients. Radiology. 1999;210(3):651–4.
143. Ryan JM, Hahn PF, Boland GW, McDowell RK, Saini S, Mueller PR. Percutaneous gastrostomy with T-fastener gastropexy: results of 316 consecutive procedures. Radiology. 1997;203(2):496–500.
144. Shin JH, Park AW. Updates on percutaneous radiologic gastrostomy/gastrojejunostomy and jejunostomy. Gut Liver. 2010;4(Suppl 1):S25–31.
145. Laasch HU, Wilbraham L, Bullen K, Marriott A, Lawrance JA, Johnson RJ, et al. Gastrostomy insertion: comparing the options--PEG, RIG or PIG? Clin Radiol. 2003;58(5):398–405.
146. Wollman B, D'Agostino HB, Walus-Wigle JR, Easter DW, Beale A. Radiologic, endoscopic, and surgical gastrostomy: An institutional evaluation and meta-analysis of the literature. Radiology. 1995;197(3):699–704.
147. Kambadakone A, Thabet A, Gervais DA, Mueller PR, Arellano RS. CT-guided celiac plexus neurolysis: a review of anatomy, indications, technique, and tips for successful treatment. Radiographics. 2011;31(6):1599–621.
148. Mercadante S, Nicosia F. Celiac plexus block: a reappraisal. Reg Anesth Pain Med. 1998;23(1):37–48.
149. Akhan O, Altinok D, Ozmen MN, Oguzkurt L, Besim A. Correlation between the grade of tumoral invasion and pain relief in patients with celiac ganglia block. AJR Am J Roentgenol. 1997;168(6):1565–7.
150. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. Anesth Analg. 1995;80(2):290–5.
151. Wang PJ, Shang MY, Qian Z, Shao CW, Wang JH, Zhao XH. CT-guided percutaneous neurolytic celiac plexus block technique. Abdom Imaging. 2006;31(6):710–8.
152. Akhan O, Ozmen MN, Basgun N, Akinci D, Oguz O, Koroglu M, et al. Long-term results of celiac ganglia block: correlation of grade of tumoral invasion and pain relief. AJR Am J Roentgenol. 2004;182(4):891–6.
153. Ischia S, Ischia A, Polati E, Finco G. Three posterior percutaneous celiac plexus block techniques. a prospective, randomized study in 61 patients with pancreatic cancer pain. Anesthesiology. 1992;76(4):534–40.
154. Ischia S, Polati E, Finco G, Gottin L, Benedini B. 1998 Labat Lecture: the role of the neurolytic celiac plexus block in pancreatic cancer pain management: do we have the answers? Reg Anesth Pain Med. 1998;23(6):611–4.

Screening for Gastrointestinal Cancers

32

Fadi Antaki, Stephanie Judd, Ziad Kanaan,
Suhag M. Patel, and Kirthi K. Lilley

Introduction

Screening refers to the identification of a harmful condition or risk factor while it is still in the asymptomatic stage of the disease. The goal of screening for malignant conditions is to allow for treatment to be initiated at an early, curable stage. In some cancers of the gastrointestinal (GI) tract, screening also allows for the identification and treatment of the precursor premalignant lesion, such as Barrett's esophagus (BE) for esophageal adenocarcinoma (EAC) or adenomatous polyps for colorectal cancer (CRC).

Wilson and Jungner [1] proposed criteria for screening in 1968, and these are still applicable today:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

(Text excerpt reprinted with permission from Wilson and Jungner [1]. http://apps.who.int/iris/bitstream/10665/37650/1/WHO_PHP_34.pdf).

Each type of cancer of the GI system fulfills these criteria to a different extent. Colorectal cancer is the best candidate for screening as it fulfills many of the above criteria: It is a common illness (Fig. 32.1) [2]; it has a relatively long asymptomatic or latent phase; multiple tests exist for early detection; the natural history is well understood; and treatment at an early stage carries an excellent prognosis. On the other hand, many other GI malignancies, such as pancreatic cancer, esophageal cancer, and liver cancer, are not ideal candidates for screening—at least not for the general population.

In this chapter, we will review each of the major cancers of the gastrointestinal system as a potential candidate for screening and summarize the current recommendations and practices related to screening.

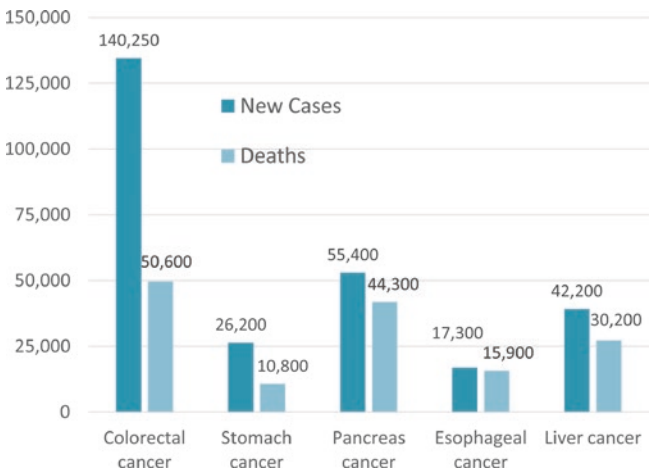


Fig. 32.1 Incidence and death rates for GI cancers in the United States in 2018 [2]

F. Antaki (✉) · S. Judd · K. K. Lilley
Division of Gastroenterology, Department of Medicine,
John D. Dingell Veterans Affairs Medical Center and
Wayne State University, Detroit, MI, USA
e-mail: fadi.antaki@va.gov

Z. Kanaan
Division of Gastroenterology, Department of Internal Medicine,
Wayne State University, Detroit, MI, USA

S. M. Patel
Division of Gastroenterology, Department of Medicine,
Unity Point Health, Allen Hospital, Waterloo, IA, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_32

Esophageal Cancer

Approximately 17,000 new cases of esophageal cancer are diagnosed per year in the United States [2]. The prognosis remains grim as nearly 16,000 individuals die of the disease each year [2]. There are two main types of esophageal cancer: squamous cell carcinoma (SCC) and esophageal adenocarcinoma (EAC). The incidence of EAC has been rapidly rising in recent years, especially in Western countries, in parallel with the rising prevalence of gastroesophageal reflux disease (GERD) and Barrett's esophagus [3]. EAC has surpassed SCC as the most common form of esophageal cancer [4]. In developing countries, esophageal SCC continues to be the most prevalent type of esophageal cancer [5].

Risk Factors

The risk factors for esophageal SCC include tobacco and alcohol consumption [6, 7], dietary factors including ingestion of food products containing N-nitroso compounds or toxin-producing fungi such as aflatoxin [8, 9], demographic and socioeconomic factors, and possibly hereditary factors [10–12]. Some of the risk factors are shared with lung cancer as well as head and neck cancer, and there is a 3–14% rate of synchronous esophageal SCC in those with head and neck cancer [13, 14]. Tylosis is a rare genetic condition that carries a 40–90% lifetime risk of esophageal SCC [15, 16]. Patients with achalasia and those with a history of caustic injury to the esophagus carry an increased risk of SCC as well [17, 18].

The main predisposing condition for EAC is Barrett's esophagus (BE), which is a metaplasia of the mucosa of the lower esophagus that arises when the normal squamous mucosa is replaced by an intestinal-type columnar epithelium. BE is thought to be a consequence of chronic GERD [19]. Other risk factors include male sex, Caucasian race, advancing age, obesity, and smoking [20–22]. There is also an increased risk for BE and EAC among first-degree relatives of patients with BE or EAC [23]. Among those with chronic GERD, the prevalence of Barrett's esophagus is as high as 15% [24, 25]. Barrett's esophagus can progress from nondysplastic metaplastic mucosa to low-grade and then high-grade dysplasia before developing into adenocarcinoma. The rate of progression to EAC is low for those with nondysplastic BE (0.2–0.5% per year) but increases in those with low- and high-grade dysplasia (0.7% and up to 7% per year, respectively) [26–31]. However, many cases of EAC occur in patients without previous complaints of GERD or a previous diagnosis of BE, which significantly limits the ability of BE surveillance programs to affect EAC mortality in the general population [32–35].

Screening Methods

Barium esophagram can help detect large neoplastic lesions; however, its sensitivity is limited for early lesions and, therefore, is no longer used as a screening test. Esophagogastroduodenoscopy (EGD) allows for direct visualization as well as sampling of the esophageal mucosa by brushings or biopsies. It can be used for screening for both SCC and EAC as well as screening for BE. In cases of BE, specific protocols have been described for tissue sampling during EGD. It is recommended to obtain four-quadrant biopsies every 2 cm in nondysplastic BE and every 1 cm in those with a history of dysplasia [36–39]. In addition, any nodular, prominent, or suspicious area(s) should be sampled separately. EGD also allows for the resection of suspicious areas within a segment of Barrett's mucosa by endoscopic mucosal resection (EMR), which provides histopathological staging and potentially treatment. Although EGD and biopsies are considered the gold standard for screening for BE, these are not without limitations: Determining the extent of BE with precision is not always easy, given the difficulty in determining the gastroesophageal junction in those with short-segment BE. Moreover, there is weak interobserver agreement for low-grade dysplasia among pathologists, and many recommend having a second pathologist concur with the interpretation. The presence of inflammation from uncontrolled GERD also makes the interpretation of dysplasia more difficult [28, 40–42].

Other modalities for screening for Barrett's esophagus that are under investigation include video capsule endoscopy of the esophagus, unsedated transnasal endoscopy, and cytological analysis using a gelatin-coated sponge called capsule sponge. For esophageal capsule endoscopy (ECE), the sensitivity and specificity for diagnosing BE in individuals with GERD are 67% and 87%, respectively [43]. Unsedated transnasal endoscopy demonstrated similar rates of detection of BE when compared to conventional EGD, and in one study higher patient satisfaction [44]. Capsule sponge is a nonendoscopic method whereby the patient swallows a gelatin capsule with mesh that is attached to a string into the stomach. Once the capsule dissolves, the mesh is exposed and collects cells that can be analyzed as it is pulled through the lower esophageal sphincter and gastroesophageal junction. According to a recent study, the capsule sponge has a sensitivity and specificity of 73% and 94%, respectively, for Barrett's esophagus spanning at least 1 cm and 90% and 94%, respectively, for BE spanning 2 cm or more [45].

Recommendations and Guidelines

For esophageal SCC, it is a common practice in many institutions to perform an EGD in patients diagnosed with head and

neck cancer as part of the so-called triple endoscopy to rule out synchronous disease [13, 46]. However, given the absence of data showing cost-effectiveness or improved survival, current US guidelines do not endorse this practice. Similarly, it might be appropriate to perform periodic screening EGDs in individuals with tylosis, achalasia, or a history of caustic injury, given the high lifetime incidence of developing esophageal SCC, although the supporting data is limited [47].

The identification of BE would allow screening practices to be focused on those with the highest risk for EAC. However, screening the general population for Barrett's esophagus or EAC is not recommended [37, 38]. Guidelines recommend screening only those at highest risk for BE, which includes males with chronic GERD with other risk factors for EAC such as central obesity, Caucasian race, family history of Barrett's or EAC, and smoking [37–39]. Female patients with chronic GERD and multiple risk factors for BE are screening candidates as well. If BE is not identified on initial screening EGD, then repeat screening is not justified as the yield is very low, unless reflux-induced esophagitis was present at the time of the initial EGD [48]. There are no randomized trials showing a decrease in either disease-specific or overall mortality from Barrett's surveillance. However, several case-control and cohort studies, and one large meta-analysis, have shown that cases of EAC detected as part of endoscopic surveillance for BE tend to present at an earlier stage and have a longer survival time [31, 32, 34, 35, 49, 50], although part of this effect could be attributed to lead-time bias and length-time bias. On the other hand, at least one case-control study found no evidence that Barrett's surveillance improved EAC survival [51]. A multicenter trial is currently underway evaluating the benefit of surveillance endoscopy for Barrett's esophagus [52]. Despite the limited data, surveillance of those with Barrett's esophagus is recommended with periodic endoscopic examinations and biopsies of the columnar epithelium [37, 38]. The suggested interval is every 3–5 years for those with nondysplastic Barrett's and more frequently for those with low- or high-grade dysplasia (every 6–12 months for low-grade dysplasia and every 3 months for high-grade dysplasia that has not been resected or ablated). Endoscopic therapies such as EMR or radio-frequency ablation (RFA) have been recommended for those with dysplasia or early superficial cancer to avoid progression to invasive adenocarcinoma [37–39].

Stomach Cancer

In the United States, gastric cancer is the 15th most common cancer, but worldwide it is the 5th most common malignancy and the 3rd leading cause of cancer-related mortality [2, 5]. Each year 26,000 new cases of gastric cancer are diagnosed in the United States, resulting in an estimated 11,000 deaths [2]. Men have twice the incidence of women [2]. The most common type of gastric cancer is adenocarcinoma and therefore will be the focus of this section. Gastric cancer is associated with a poor prognosis, with an overall 5-year survival of about 20–30%, except in Japan where rates above 70% have been reported, possibly due to the elevated number of early neoplastic lesions detected by screening [2, 5, 53, 54]. The overall incidence of gastric cancer has been declining over the past few decades, and this has been, in part, attributed to the declining rates of *Helicobacter pylori* infection [55].

Risk Factors

The role of *Helicobacter pylori* infection in predisposing to gastric adenocarcinoma is well established [56], and it has been classified by the World Health Organization (WHO) as a Class I carcinogen [57]. By some estimates, more than 70% of cases of gastric cancer worldwide are linked to *H. pylori* infection [58]. Eradication of *H. pylori* infection has been shown to correlate with a decreased risk of gastric cancer (46% lower risk in a recent large meta-analysis) [59]. However, other factors besides *H. pylori* infection play a role in the development of gastric cancer, as incidence of gastric cancer varies widely from country to country [60, 61]. Other risk factors for gastric adenocarcinoma include tobacco and alcohol consumption, low socioeconomic status, obesity, family history of gastric cancer, foods high in nitrates as well as high salt diet, and prior history of gastrectomy [62]. Genetic conditions such as Lynch syndrome, familial adenomatous polyposis (FAP), Cowden syndrome, Peutz-Jeghers syndrome, and Li-Fraumeni syndrome also increase the risk of gastric adenocarcinoma [63–68].

Histologically, gastric adenocarcinoma has been divided into two broad categories that include the diffuse type and the intestinal type, which are based on the Lauren histological classification [69]. The Correa cascade describes the progression of histological changes seen in the intestinal type of gastric cancer with *H. pylori* playing a key role in the initiation of the cascade [70]. Persistent inflammation over time leads to the development of atrophic gastritis, which subsequently leads to intestinal metaplasia, dysplasia, and eventually gastric carcinoma [71]. Chronic atrophic gastritis and intestinal metaplasia are known premalignant conditions that have an annual progression rate of less than 1% [72]. Gastric intestinal metaplasia (GIM) is a condition in which the gastric epithelium is largely replaced by either small intestinal-type epithelium or colonic-type epithelium. The most commonly used classification of GIM is described by Jass and Filipe, which classifies metaplasia into complete (type I) and incomplete types (types II and III) [73, 74]. Although incomplete types have been associated with higher risk of progression to gastric cancer, there is no current standardized

way to implement the histological subtypes in clinical practice [75], and often, it is not reported by pathologists [76]. Due to the low risk of progression to gastric cancer in the US population, surveillance is currently not recommended by the American Society for Gastrointestinal Endoscopy (ASGE) for this condition unless there are other coexisting risk factors, such as family history of gastric cancer or Asian descent [77]. In contrast, European guidelines have recommended endoscopic surveillance every 3 years for those with extensive gastric atrophy and/or intestinal metaplasia [75].

Low-grade dysplasia (LGD) and high-grade dysplasia (HGD), if found on histology, are also associated with increased risk of progression to gastric carcinoma of the intestinal subtype [78, 79]. For patients with LGD, periodic surveillance is recommended starting within 1 year of diagnosis. Consideration for stopping surveillance can be made after two consecutive negative endoscopies [75, 77, 80]. In patients with HGD and endoscopically defined lesion, immediate surgical or endoscopic resection should be considered given the high risk of progression to adenocarcinoma [78]. Immediate histological re-evaluation with extensive biopsies with subsequent surveillance every 6–12 months should be considered in those with HGD without an endoscopically identified lesion [75, 77].

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant disease that involves mutation in CDH1 (E-cadherin) gene and is also associated with predisposition to gastric cancer [81]. Due to the high penetrance rate of gastric cancer, prophylactic total gastrectomy, rather than screening, is recommended to those affected with HDGC [82].

Pernicious anemia is also associated with an increased risk of gastric adenocarcinoma as well as gastric carcinoid tumors. A large case-control study found that patients with pernicious anemia were at increased risk for noncardia gastric adenocarcinoma and gastric carcinoid tumor with odds ratios (ORs) of 2.18 and 11.43, respectively [83]. Current ASGE guidelines recommend a single diagnostic upper endoscopy performed at the time of diagnosis of pernicious anemia to screen for gastric cancer as the risk of cancer is highest within a year of diagnosis [77]. Diagnostic endoscopy is also recommended if upper gastrointestinal symptoms develop in the patients with pernicious anemia [77].

Screening Methods

Due to the low incidence in North America, screening for gastric cancer is not recommended. Population-based screening is practiced in some countries in East Asia with higher gastric cancer incidence, particularly Japan and Korea. Although there are various noninvasive and invasive modalities for gastric cancer screening, upper GI endoscopy and contrasted radiological studies, particularly X-ray photofluorography, are the most commonly utilized screening modalities. Other less commonly used noninvasive tests include serological screening with serum pepsinogen test, *H. pylori* antibody, or Gastrin 17.

For screening tests to be considered effective, they must not only reduce mortality rate but also be cost-effective when implemented in population-based screening programs. Most of the studies performed to evaluate the effectiveness of these screening tools for gastric cancer are observational studies performed in high prevalence areas.

Contrasted Radiographic Tests: X-Ray Photofluorography (Upper Gastrointestinal Series)

In Japan, X-ray photofluorography, also known as upper GI series (UGIS), is the initial test of choice for population-based gastric cancer screening and opportunistic screening. UGIS is performed by swallowing a barium meal followed by a series of X-ray films that image the stomach at various angles. Although there are no randomized controlled trials addressing the effect of UGIS for gastric cancer screening, case-control studies, mainly from Japan, have shown reduction in gastric cancer mortality by 40–60% [84–88]. Estimated sensitivity and specificity of UGIS based on these studies ranged from 60 to 80% and 80 to 90%, respectively [89].

Endoscopy

While upper endoscopy or esophagogastroduodenoscopy (EGD) has a well-established role in diagnosis, staging, treatment, and palliation of gastric cancer, its implementation for screening is still evolving. A mortality reduction of 30% was reported in one case-control study of patients screened with endoscopy as compared to those who were never screened [90]. Other studies have compared UGIS and EGD and showed higher detection rates with EGD and therefore concluded that EGD was a more effective screening tool for gastric cancer based on comparison of sensitivity, specificity, and positive predictive value [91, 92]. An additional potential benefit of an EGD over an UGIS is the ability to perform a therapeutic resection at the same time as screening.

Serological Testing: Serum Pepsinogen Test and *Helicobacter pylori* Antibody

Serological testing is currently not recommended as an initial screening test for gastric cancer in any of the international guidelines. However, it may still have a role in identifying high-risk groups. There are three serological methods of

screening, which include the serum pepsinogen testing, *H. pylori* antibody screening, or a combination of both tests. Due to low specificity (73%), screening using serum pepsinogen testing is not recommended [93]. The combination method is used in Japan to help identify high-risk groups who may benefit from endoscopic screening [94].

Recommendations and Guidelines

Due to the low incidence of gastric cancer and the lack of proven cost-effectiveness, there are no national guidelines for gastric cancer screening in the United States and Europe. Screening may be considered in first-generation immigrants from high-risk regions, especially for those with a family history of gastric cancer [95]. Japan and Korea are the only two East Asian countries to have nationwide screening programs, and this is due to the higher prevalence of gastric cancer in this region. The Japanese guidelines recommend annual screening for those 40 years of age or over with UGIS for population-based screening [89]. Other methods of gastric cancer screening including serum pepsinogen test, *H. pylori* antibody, and endoscopy were evaluated; however, due to insufficient evidence, these methods were not recommended for population-based screening, but can be used for opportunistic screening [89]. More recently, the Japanese guidelines on gastric cancer screening were revised and have recommended either UGIS or EGD as initial screening test for those aged 50 and older. Repeat screening is recommended every 2–3 years instead of every year as in the 2008 guidelines. These changes were made as a result of declining incidence of gastric cancer in the 40–50 age group as well as large amount of costs associated with mass screening [94].

Guidelines for gastric cancer screening have existed in Korea since 2001. Biennial screening is offered in Korea to those aged 40 years or older with either upper gastrointestinal series (UGIS) or endoscopy [96]. Despite the high incidence of gastric cancer, there is no national program for gastric cancer screening in China at this time [60].

Colorectal Cancer

Colorectal cancer (CRC) is one of the most common cancers and often develops in a multistep process starting with precancerous polyps (colonic adenomas) [97, 98]. In the United States alone, 140,000 new cases of CRC and approximately 47,500 deaths are expected annually [2]. Worldwide, CRC is the third most common cancer in men (746,000 cases, 10.0% of the total cancers) and the second in women (614,000 cases, 9.2% of the total cancers) [5]. More than half of these cases occur in developed regions, and there is a significant tenfold incidence variation across the world [5].

Risk Factors

The risk of colorectal cancer development is largely acquired, although genetic factors play a role. The most studied factors, which are also integrated into current screening recommendations, include age and family history of CRC [99]. Among those with family history, the risk of CRC is highest in people with multiple first-degree relatives or relatives who have developed colorectal cancer at a relatively young age [100]. The increase in lifetime risk related to family history is usually between 2- and 6-fold [100]. In the United States, CRC has higher incidence and mortality in African Americans as compared to Caucasians [101]. The lifetime risk of CRC is almost equal in men and women; however, the prevalence of advanced adenomas is higher in men than women, and adenomas are found at an earlier age in men than women [102–104].

Other factors that convey an increased risk of CRC include obesity and elevated body mass index (BMI), smoking, as well as dietary factors (high intake of red and processed meats, highly refined grains and starches, and sugars) [105]. There are also several factors that are known to decrease the risk of CRC. Medications such as aspirin [106], COX-2 inhibitors (such as celecoxib and rofecoxib) [107, 108], and postmenopausal hormones in women [109] have been associated with substantial reductions in colorectal cancer risk, though their use is limited by their own associated risks [110].

Average-Risk Populations

Individuals are considered to be at average risk when no previously identified CRC risk factors are identified. Around three quarters of all colorectal cancers are diagnosed in average-risk persons, and approximately 90% occur during the sixth decade of life or later—although the prevalence of CRC is increasing in the younger population.

High-Risk Populations

A prior history of CRC increases the risk of another primary cancer by 1.4 times as compared to the rate in the general population [111]. Additionally, a history of adenomatous colorectal polyps also increases the risk of CRC, especially if the polyps are multiple, large, or have villous architecture [112]. Patients with ulcerative colitis (UC) and Crohn's (CD) colitis are at increased risk of developing CRC. Ulcerative colitis, in particular, carries a high risk for malignant transformation, with UC patients being up to 30 times more likely to develop CRC and 3 times more likely to die from CRC compared with the

general population [113]. Risk factors for CRC in UC patients include disease duration greater than 8 years, pancolitis, biopsy-proven colonic dysplasia, and the presence of primary sclerosing cholangitis affecting the liver [114]. Those with Crohn's colitis also have a 4.5-fold higher relative risk of developing CRC than the general population [115].

High-Risk Genetic Syndromes

Lynch syndrome, also known as hereditary nonpolyposis colon cancer (HNPCC), is one of the most common hereditary colon cancer syndromes and accounts for approximately 3% of all CRC [101]. It is an autosomal dominant syndrome that is caused by mutations in DNA mismatch repair genes and confers a lifetime risk of colorectal cancer of approximately 80% with a mean age at diagnosis of 44 years [101]. Colorectal adenomas usually develop by age 20–30 years and are thought to progress to colorectal cancer more quickly than sporadic adenomas [101]. Familial adenomatous polyposis (FAP), another autosomal dominant genetic syndrome, accounts for about 1% of all CRC cases and is caused by mutations in the APC gene [116]. Hundreds to thousands of polyps occur throughout the colon beginning in adolescence [116]. Tumors develop beginning in the 20s, and development of CRC is almost universal in these individuals, usually before age 50 [116]. Other forms of FAP include Gardner syndrome and Turcot syndrome, which are associated with desmoid tumors, sebaceous or epidermoid cysts, osteomas (especially of the mandible), and fibromas in Gardner's [117]; and brain tumors (primarily medulloblastomas and gliomas) in Turcot's [117]. Other less common syndromes include the serrated polyposis syndrome, the juvenile polyposis syndrome, and Peutz-Jeghers syndrome.

Screening Modalities

Many CRC deaths could be prevented if precancerous polyps were detected with regular screening and removed prior to the development of invasive cancer [118, 119]. Detection of precancerous lesions, such as colorectal adenoma, is key to reducing the incidence of CRC [118, 120]. No accurate, simple, broadly applicable screening test currently exists for the detection of colorectal adenomas that can identify candidates for intervention (endoscopic removal). Currently available CRC screening tools are divided into:

1. Structural tests that detect early CRC as well as precancerous polyps. Such tests have disadvantages, such as need for laxative preparation, which can complicate patient compliance, elevate costs, and potentially put patients at risk for a complication.
2. Stool/fecal-based tests that focus more on early detection of asymptomatic CRC to improve mortality, without affecting incidence.

Colonoscopy

Colonoscopy is an endoscopic procedure that allows for the evaluation of the entire colon. It allows for screening for existing CRC as well as for resection of precancerous polyps. To date, screening colonoscopy has not been evaluated in randomized controlled trials with CRC incidence or mortality as primary endpoints. However, many case-control and cohort studies have shown that colonoscopy is associated with a reduction in CRC-related mortality (Table 32.1) [119, 121–128]. A study from the US Department of Veterans Affairs showed a protective effect for colonoscopy from CRC (OR 0.43 [0.30–0.63]) [119].

Table 32.1 Studies of colonoscopy for colorectal cancer (CRC) screening

Study	Year	Design	Screened cases	Controls	Follow-up (years)	Effect on CRC
Baxter et al. [122]	2009	Case-control	10,292	51,460	8	Decrease in CRC mortality
Kahi et al. [126]	2009	Prospective	715	SEER database	18	Decrease in CRC incidence Nonsignificant decrease in CRC mortality
Singh et al. [123]	2010	Retrospective cohort	54,803	General population	10	Decrease in CRC mortality
Brenner et al. [127]	2010	Retrospective cohort	586	2,701	10	Decrease in incidence of advanced neoplasia
Brenner et al. [128]	2011	Case-control	1,688	1,932	10	Decrease in CRC incidence Nonsignificant change in CRC mortality
Manser et al. [124]	2012	Prospective controlled	1,912	20,774	6	Decrease in CRC incidence and mortality

SEER Surveillance, Epidemiology, and End Results

Additionally, two large Canadian studies reported an association between colonoscopy and decreased CRC mortality, with an OR of 0.69 [0.63–0.74] for the Ontario case-control study [122] and a risk reduction of 29% for the Manitoba retrospective cohort study [123] . However, those retrospective studies showed a strong left-sided effect with lower efficacy against right-sided cancers [122, 123]. The largest prospective study to date showed a 53% reduction in CRC with colonoscopy [125]. It is currently considered the "gold standard" for CRC screening [118, 125, 129]. Colonoscopy has some disadvantages including high patient noncompliance, the need for sedation, morbidity such as colon perforation [130], need for bowel cleansing, and expense [131]. Adverse events associated with colonoscopy increase with age [132]. Screening colonoscopy is recommended every 10 years, although if precancerous polyps are resected, then shorter interval follow-up is required [133].

Flexible Sigmoidoscopy

Flexible sigmoidoscopy is an endoscopic procedure that involves the examination of the distal colon, from the rectum up to the splenic flexure. When used as a screening test, it is usually repeated every 3–5 years. If adenomas are detected by sigmoidoscopy, a follow-up colonoscopy is recommended. Randomized controlled trials have shown a decrease in CRC-related mortality, mainly for distal CRC with flexible sigmoidoscopy (Table 32.2) [134–140]. Despite this, its use in the United States has significantly declined as it has been mainly replaced by screening colonoscopy [141–143]. However, screening sigmoidoscopy continues to be used in many parts of the world.

Double-Contrast Barium Enema

The use of double-contrast barium enema (DCBE) has significantly decreased and is only an alternative in patients who cannot undergo colonoscopy or where a full colonoscopic examination to the cecum is not completed [144].

Computed Tomography Colonography

Also known as virtual colonoscopy, computed tomography colonography (CTC) has the advantages of being noninvasive and not requiring sedation. The risk for test-related complications is very low [145, 146]. CTC has a sensitivity of 91% and specificity was 85% for adenomas 10 mm or larger. Both sensitivity and specificity decrease as the polyp size decreases [147]. Limitations of CTC include the need for a bowel preparation, follow-up colonoscopy for positive studies, the high prevalence of extra-colonic findings (up to 16%) that require further work-up, and the risks related to radiation exposure, which includes the potential for leading to additional cancers [148]. In the United States, CTC is not widely used as a screening test, mainly due to lack of insurance coverage.

Fecal Occult Blood Tests

Fecal occult blood testing (FOBT) works by detecting early cancer and, therefore, decreasing CRC-specific mortality. FOBT includes guaiac-based tests (gFOBT) and fecal immunochemical tests (FIT) [148]. These tests are inexpensive, easy to administer, and require no bowel preparation. Several large randomized controlled trials have previously

Table 32.2 Randomized control trials of colorectal cancer (CRC) screening by sigmoidoscopy

Study	Year	Screened cases	Controls	Follow-up (years)	Effect on CRC
Selby et al. [134]	1988	5,156	5,557	16	Decrease in CRC mortality OR = 0.41 (95% CI: 0.25–0.69)
Kavanagh et al. [135]	1998	3,195	21,549	8	Decrease in CRC incidence Nonsignificant change in CRC mortality
Thiis-Evensen et al. [136]	1999	400	399	13	Decrease in CRC incidence Nonsignificant change in CRC mortality
Hoff et al. [137]	2009	13,653	41,092	7	Nonsignificant change in CRC incidence or mortality
Atkin et al. [138]	2010	57,099	112,939	11	Decrease in CRC mortality HR = 0.69 (95% CI: 0.59–0.82)
Segnan et al. [139]	2011	17,148	17,144	11	Decrease in CRC incidence Nonsignificant change in CRC mortality
Schoen et al. [140]	2012	77,445	77,455	12	Decrease in CRC incidence Decrease in CRC mortality, RR = 0.74 (95% CI: 0.63–0.87)

OR odds ratio, *CI* confidence interval

Table 32.3 Randomized controlled trials of colorectal cancer (CRC) screening by guaiac-fecal occult blood testing (FOBT)

Study	Country	Age range	Year	Cohort	Follow-up (years)	Frequency	Effect on CRC mortality RR 95% CI
Mandel et al. [149]	United States	50–80	1993	46,551	13	Annual	0.67 (95% CI 0.50–0.87)
						Biennial	0.94 (95% CI 0.68–1.31)
Kewenter et al. [150]	Sweden	60–64	1994	68,308	8.3	2 screens[a]	0.88 (95% CI 0.69–1.12)
Hardcastle et al. [151]	United Kingdom	45–74	1996	152,850	7.8	Biennial	0.86 (95% CI 0.74–0.99)
Kronborg et al. [152]	Denmark	45–75	1996	61,933	10	Biennial	0.82 (95% CI 0.68–0.99)

RR relative risk, *CI* confidence interval
[a]16–24 months apart

shown reductions in CRC mortality by using annual gFOBT (up to 30%) (Table 32.3) [149–152]. In the follow-up of one of these studies, the effect of screening by gFOBT on CRC mortality persisted after 30 years of follow-up [153]. Dietary factors can lead to both false positives and false negatives with gFOBT, while FIT is more accurate as it is more specific to human hemoglobin. FIT is currently the preferred test for occult blood in stool and is used annually. As in all other screening tests, a positive test requires a follow-up colonoscopy. FIT tests have good sensitivity and specificity for CRC (up to 91% and 94%, respectively) and a lower sensitivity of 20–67% for adenomatous polyps [154, 155].

Stool-Based DNA Testing

Attempts to identify specific DNA mutations associated with CRC in exfoliated colonocytes in the stool have been undertaken. Early generations of these tests were very limited due to low sensitivity and specificity [156]. A second-generation multitargeted DNA test for CRC (Cologuard®, Exact Biosciences, Madison, WI) was found to have excellent sensitivity (92.3%) for detection of cancer stages I–IV with a specificity of 87% [157]. Currently, Cologuard is commercially available in the United States and is approved by Medicare for screening of average-risk patients every 3 years, although no long-term randomized trial has shown it to be an effective option as a screening modality.

Other Screening Modalities

Carcinoembryonic antigen (CEA) assay is the most popular assay for clinical monitoring. It has been used for postoperative surveillance and for monitoring response to therapy. CEA, however, lacks sufficient sensitivity and specificity as a screening test [158]. Methylated septin 9 has been reported to have good sensitivity and specificity for CRC, up to 72% and 80%, respectively, but with a limited ability to detect colorectal adenomas [159]. In April 2016, the US Food and Drug Administration (FDA) approved Epi proColon® (Epigenomics AG, Seattle, WA), which measures serum methylated septin 9 DNA, as a noninvasive CRC screening test, for average-risk patients who are not willing to get screened by colonoscopy or FIT.

Other markers in development include CSA (colon cancer-specific antigen)-1, 2, and 3, colon cancer-secreted protein (CCSP)-2 [160], galectin-3-ligand, and haptoglobin-related glycoprotein. Recently, CA11-19 emerged as a promising serologic tumor marker for the diagnosis of CRC with a sensitivity of 98% and specificity of 84% [161].

Comparison of Screening Methods

To date, there has been no published prospective study comparing the different screening modalities for CRC screening, although two large randomized trials are currently underway comparing the efficacy of FIT to screening colonoscopy in reducing mortality from CRC. One study found that adherence with colorectal cancer screening was the highest when patients were given an option between FOBT and colonoscopy, rather being advised to have a specific test [162].

Future Direction

The greatest impact of any future screening test would be disease detection before development of invasive cancer, i.e., adenoma detection. Many studies have recently explored microRNAs (miRNAs) as biomarkers for early cancer detection and screening. MicroRNAs are small noncoding RNA molecules that regulate gene expression posttranscriptionally by binding to the 3′ untranslated regions of target messenger RNAs, playing a crucial role in the regulation of protein expression. MicroRNAs are involved in many cellular processes and have been associated with various diseases, including cancer [163]. To date, studies looking at miRNAs and CRC are inconclusive and contradictory. Some investigators have found plasma miRNA to be useful, whereas others have not. Problems with studies include small sample sizes, varying techniques of normalization, methods of analysis, and use of pooled samples [164–167].

Guidelines for Screening

Average-Risk Groups

Two major US guidelines, from the American Cancer Society (ACS) and Multi-Society Task Force (MSTF) and the US Preventive Services Task Force (USPSTF), were released in 2008 [168, 169]. Other guidelines include those of the American College of Gastroenterology (ACG) and the American College of Physicians (ACP). All US guidelines endorse screening of average-risk patients for CRC starting at age 50 until age 75 (USPSTF) or until life expectancy is less than 10 years. There have been some suggestions to start screening of African Americans at age 45 [170], although this has not been formally accepted yet. Most of the US guidelines recommend screening with one of the options discussed earlier, either FOBT, sigmoidoscopy, or colonoscopy. The ACS/MSTF also include fecal DNA and CTC. The ACG guidelines endorse colonoscopy as the preferred screening test.

High-Risk Groups

High-risk groups consist of patients with personal history of CRC, prior history of premalignant colorectal polyps (adenomas or sessile serrated polyps), inflammatory bowel disease (IBD) (either UC or Crohn's colitis), family history of CRC, or those with genetic syndromes predisposing to CRC. In patients with prior history of CRC, periodic surveillance with colonoscopy is recommended [171]. In those with a history of premalignant polyps, a repeat colonoscopy is recommended at 1-, 3-, 5-, or 10-year intervals depending on polyps' number, size, and histology [133]. In patients with inflammatory bowel disease, UC or Crohn's colitis, the recommendation is to perform surveillance colonoscopy starting 8 years after diagnosis and every 1–2 years afterward [168]. Screening with colonoscopy is the preferred option in patients with a significant family history of colon cancer or in those with a genetic predisposition to CRC [168]. Generally, a colonoscopy should be performed at an earlier starting age and shorter intervals than an average-risk population.

In summary, for average-risk patients aged between 50 and 75, there is broad consensus to recommend CRC screening using one of the available modalities.

Liver Cancer

Worldwide, approximately 700,000 cases of liver cancer are diagnosed annually with 600,000 deaths related to the disease each year, making it the third most common cause of cancer-related death [5, 172]. It is estimated that approximately 42,000 new cases will be diagnosed in the United States in 2018, resulting in 30,000 deaths from primary liver cancer and intrahepatic bile duct cancer [2]. There are profound variations in the incidence of hepatocellular carcinoma (HCC) throughout the world. The incidence of HCC is rising in developing countries, and while a nonsignificant increase was noted in the United States in recent analysis, the mortality of HCC continues to increase both in the United States and around the world [173, 174].

Identifying High-Risk Population

HCC develops in the setting of chronic liver disease. The most common risk factors for HCC include chronic viral hepatitis (hepatitis B virus [HBV] and/or hepatitis C virus [HCV]), alcoholic cirrhosis, inherited errors of metabolism such as hereditary hemochromatosis and alpha-1 antitrypsin deficiency, Wilson's disease, and stage 4 primary biliary cirrhosis. Exposure to aflatoxin is another risk factor for HCC [175–177].

Whether to include a patient with any chronic liver disease in a screening program depends upon the risk of HCC, which in turn depends upon the incidence of HCC. Ideally, any screening intervention should be cost-effective. Published models have shown that the HCC surveillance is cost-effective, specifically if the incidence of HCC is above a certain threshold [178, 179].

Chronic Hepatitis B

HCC can develop in hepatitis B carriers even in the absence of liver cirrhosis. In fact, approximately 30–50% of patients with chronic hepatitis B who develop HCC do not have cirrhosis [180]. The American Association for Study of Liver Diseases (AASLD) guidelines recommend an HCC incidence threshold of 0.2% per year for chronic hepatitis B to be considered for a screening program to make it cost-effective [181]. The following groups of patients with chronic hepatitis B: Asian men over the age of 40, Asian women over the age 50, hepatitis B carrier with family history of HCC, Africans as well as African Americans, and those who have developed liver cirrhosis have been shown to exceed this threshold and therefore are at increased risk of developing HCC [181].

Risk factors for HCC in chronic hepatitis B carriers include male sex, increasing age, higher HBV DNA, HBeAg and HBV DNA positivity, core-promoter mutations, co-infection with human immunodeficiency virus (HIV), and presence of cirrhosis. Risk scores [182, 183] have been developed to identify the at-risk population, but these scoring systems are not yet validated or used in clinical practice.

Risk of HCC persists in Asians who are hepatitis B carriers even after seroconversion (development of HBeAb or

loss of HBsAg), and hence, they should continue HCC screening [182, 184]. Risk of HCC declines significantly in non-Asians who are chronic carriers and have long-term inactive replication or those with loss of HBsAg [185, 186]. There is insufficient data to determine if HCC screening should be continued in this population.

Chronic Hepatitis C

In contrast to chronic hepatitis B, HCC development is seen in chronic hepatitis C patients only after they develop cirrhosis. However, limited data does show that HCC development is possible in chronic hepatitis C patients with bridging fibrosis in the absence of cirrhosis [187]. The AASLD recommends enrolling patients with chronic hepatitis C for HCC screening once the incidence of HCC rises above the threshold of 1.5% per year to make it cost-effective [181]. This threshold is exceeded in patients with chronic HCV cirrhosis but not in patients with chronic hepatitis C without cirrhosis [187]. Patients with liver cirrhosis who have cleared hepatitis C should continue HCC surveillance [181].

Therefore, to enroll a patient with chronic hepatitis C in a screening program, accurate assessment of the degree of liver fibrosis and presence of cirrhosis is required. Several noninvasive markers, formulas, and imaging modalities [188–193] have been developed to help predict fibrosis or cirrhosis without obtaining liver biopsy, which is currently the gold standard. These tests are not fully validated and should be used with caution. Transient elastography is a new technology, which is increasingly being used to predict the presence of liver cirrhosis or advanced fibrosis [194–196]. More data is required prior to making any definitive recommendations about the use of this technology.

Alcoholic Liver Disease

Excess alcohol consumption increases the risk of development of HCC when it leads to liver cirrhosis [197]. Studies that aimed to identify incidence of HCC in alcoholic cirrhosis probably overestimated the true incidence since these studies predated hepatitis C virus identification. In a study published in 2000, alcoholic liver disease was noted to be present in 35.1% of patients with HCC [198], while another study suggested that the 5-year cumulative HCC risk was approximately 1% in patients with alcoholic cirrhosis [199]. These studies reveal that there are wide variations in HCC occurrence in this patient population. The true incidence of HCC in alcoholic cirrhosis still remains unknown, but it is probably high enough to warrant screening for HCC.

Cirrhosis Due to Other Causes

In general, cirrhosis increases the risk of HCC. Risk factors for development of HCC in patients with cirrhosis from any cause include age >40 years, male sex, obesity, diabetes, cigarette smoking, family history of HCC, hepatic venous outflow obstruction, and aflatoxin exposure, in addition to other risk factors mentioned previously [200–202].

An HCC incidence cutoff of 1.5% per year is suggested in patients with liver cirrhosis due to any cause other than chronic hepatitis B for consideration for enrollment in a screening program. However, there are a few areas where definitive recommendations cannot be made due to lack of accurate evidence. For instance, in patients with cirrhosis related to NAFLD (nonalcoholic fatty liver disease), the true incidence of HCC is unknown. Similarly, in patients with autoimmune hepatitis-related cirrhosis, HCC incidence was noted to be about 1.1% per year, which is below the suggested cutoff [203]. In view of the limited data, HCC screening is recommended for patients with liver cirrhosis from any cause.

Screening Modalities

Serological Tests

Various serological tests have been evaluated for HCC screening. One such test is alpha fetoprotein (AFP). Sensitivity of AFP for HCC screening depends upon the cutoff value chosen. Sensitivity of AFP is only about 60% when a cutoff value is set at 20 ng/mL [204] and decreases if a higher cutoff value is used (to improve specificity), thus defeating the purpose of using AFP as a screening test. Additionally, smaller HCCs may not secrete clinically detectable levels of AFP, and early cancers may be missed if AFP alone is used for screening [205]. Significantly elevated AFP may suggest poorly differentiated cancers, which are frequently too advanced for any therapeutic resection to be considered. Studies have shown that neither AFP nor des-gamma-carboxy prothrombin alone is optimal for HCC screening [206]. Since AFP level can be elevated in certain nonmalignant conditions and could be normal in some HCC patients [207], the AASLD no longer recommends use of AFP as a screening test.

Other biomarkers that have been evaluated for HCC screening include ratio of glycosylated AFP to total AFP, glypican-3, alpha fucosidase, vascular endothelial growth factor (VEGF), osteopontin, prostaglandin E2, HSP-70, and plasma microRNAs, but definite recommendations cannot be made at present due to limited data.

Radiological Tests

The most commonly used radiological tool for HCC screening is ultrasound (US). Hepatic ultrasound has sensitivity as high as 94% and specificity that approaches 90% for HCC screening, although it is less sensitive for early-stage HCC [208]. Higher detection rates have been noted with combined use of ultrasound and AFP, but this strategy also raises the cost of care and false-positive rates. Performance of other imaging modalities such as CT scan and magnetic resonance imaging (MRI) has been evaluated in diagnostic studies, once suspicion for HCC is raised by other methods. Exact performance characteristics of these modalities for HCC screening are therefore unknown. In general, CT scan has a good sensitivity for HCC, especially when dynamic CT scan ("triple phase") is used; however, its cost and repeated exposure to radiation limit its use as a screening modality. A recently published small, randomized controlled trial compared performance and cost of twice-a-year ultrasound to once-a-year triple-phase CT scan [209]. This trial showed that the biannual ultrasound was marginally more sensitive and less costly for detection of early HCC compared with annual CT scan. However, HCC-related mortality remained high. Magnetic resonance imaging is highly sensitive for detection of HCC; however, it is not cost-effective as a screening test and is currently mainly used to confirm a suspected ultrasound diagnosis.

Screening Interval

The interval for screening is usually determined by the tumor growth rates, and an interval of 6–12 months is recommended based on tumor doubling time. A community-based randomized trial compared HCC surveillance at 4-month vs. 12-month interval in chronic viral hepatitis and showed that the 4-month interval detected more patients with very early-stage HCC but overall survival was not different between the groups [210]. A multicenter randomized trial from Europe compared 3-month vs. 6-month screening for HCC in patients with cirrhosis using ultrasound and found that the overall HCC detection was similar in both groups [211]. A multicenter study from Italy reported similar survival rates in patients with cirrhosis screened at 6-month vs. 12-month interval [212]. A retrospective study has reported improved early HCC detection rates and patient survival rates with semiannual screening than annual screening [213]. The AASLD recommends HCC surveillance using ultrasound, with or without AFP, every 6 months.

Evidence of Benefit from Screening

Improvement in 5-year survival rates to greater than 60% has been noted with tumor resection or liver transplantation if HCC is detected early, which is in contrast to only about 32% for advanced tumors [214]. Evidence of benefit of a screening program for HCC comes from a large randomized controlled trial from China involving 18,816 patients with current or prior hepatitis B. The trial compared 6-month surveillance with AFP and liver ultrasound to no surveillance and showed a 37% reduction in HCC-related mortality in the surveillance group in spite of suboptimal adherence (less than 60%) to recommended surveillance [215].

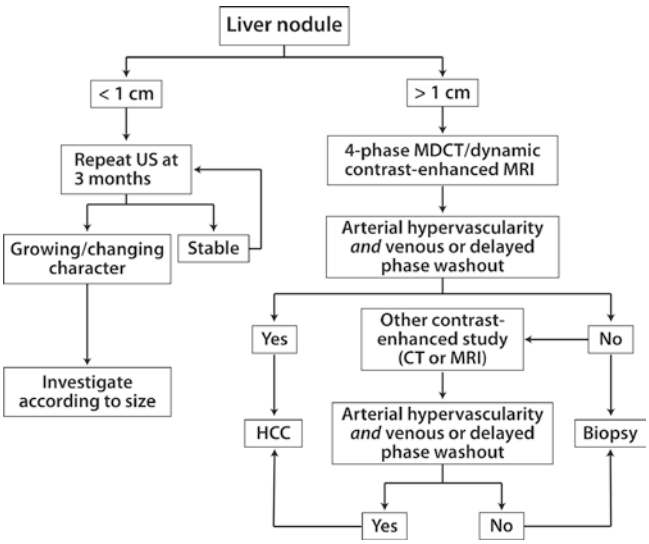


Fig. 32.2 Diagnostic algorithm for suspected HCC. CT computed tomography, MDCT multidetector CT, MRI magnetic resonance imaging, US ultrasound. (Modified from Bruix et al. [181]. Under terms of https://creativecommons.org/licenses/by/2.5/)

Summary and Recommendations

In summary, screening is recommended for those at high risk for developing HCC (Fig. 32.2). Ultrasound is the preferred modality and should be performed every 6 months. Additionally, patients on liver transplant waiting lists should also be screened, as those with HCC are given priority for transplant in many countries, including the United States.

Pancreatic Cancer

Pancreatic cancer accounts for 4% of all cancers diagnosed, affecting approximately 330,000 individuals worldwide [5]. It is the second most commonly diagnosed cancer of the digestive system, with 55,300 newly diagnosed cases in the United States in 2016 [2]. The incidence of pancreatic cancer rises sharply after age 45 and is nearly equivalent between both sexes [2], but appears to be modestly higher in blacks

(14.8 per 100,000) than whites (8.8 per 100,000) [216]. The prognosis of pancreatic cancer remains grim, and approximately 44,300 individuals were expected to die from the disease in 2018 [2]. In the United States, pancreatic cancer is the fourth most common cause of cancer-related death and is the seventh most common cause worldwide [2, 5].

Risk Factors

Pancreatic cancer is slightly more common in men than in women, is usually diagnosed in those greater than age 45, and has a higher incidence in some ethnic groups such as African Americans, Ashkenazi Jews, and Pacific Islanders [217]. As in many gastrointestinal malignancies, the risk of pancreatic cancer appears to be related to a combination of genetic, environmental, and lifestyle factors. The genetic risk factors include familial pancreatic cancer, hereditary pancreatitis, and other genetic syndromes. Other risk factors include nonhereditary chronic pancreatitis, premalignant pancreatic cysts, and lifestyle factors such as cigarette smoking, obesity, diabetes mellitus, and lack of physical activity.

While most pancreatic cancers appear to be sporadic, approximately 5–10% of individuals with pancreatic cancer can identify a first-degree relative with the disease [218], and a hereditary component may be present in up to 17% of pancreatic cancers [219]. Familial pancreatic cancer is defined as an inherited susceptibility to the development of pancreatic cancer with two or more first-degree relatives with the disease, in the absence of known genetic mutations or cancer syndromes. Individuals born to families with familial pancreatic cancer are estimated to carry up to a 13% increased risk of developing the disease, and those with first-degree relatives diagnosed prior to age 50 appear to carry the greatest risk [220]. According to data from the National Familial Pancreas Tumor Registry, the observed-to-expected ratio of pancreatic cancer was 6.4 for individuals with 2 affected relatives, which increased to 32 if 3 relatives were affected [221].

Autosomal dominant hereditary pancreatitis is a rare illness and is usually caused by mutations in serine protease 1 gene (PRSS1) that encodes cationic trypsinogen. Approximately two-thirds of cases are caused by mutations R122H and N29I [222]. By some estimates, those affected carry a 40% lifetime risk of developing pancreatic cancer [223], with one study suggesting a 54% risk by age 75 years [224]. Cigarette smokers with autosomal dominant hereditary pancreatitis appear to be at a significantly higher risk [225]. Recommendations from the Consensus Committees of the European Registry of Hereditary Pancreatic Diseases include screening these individuals for pancreatic cancer starting at age 40, though no specific recommendations were given regarding the interval or modality of screening [226].

A substantial number of rare genetic syndromes are also associated with pancreatic cancer. The highest risk is in those with Peutz-Jeghers syndrome (PJS), which is characterized by germline mutations in gene STK11. These individuals carry up to a 36% lifetime risk of pancreatic cancer with a relative risk of 132 [227]. Other genetic syndromes such as Lynch syndrome, familial adenomatous polyposis (FAP), and ataxia-telangiectasia are also associated with a modestly increased risk of pancreatic cancer [228–230]. Cystic fibrosis, an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, may also be associated with an increased risk of pancreatic cancer, though studies are conflicting. One study described an increased risk of pancreatic cancer in their cohort with an odds ratio of 61 [231], but others studies, including one evaluating nearly 29,000 patients with cystic fibrosis, found only a 2.6-fold increased risk [232].

In addition to the heritable conditions and syndromes, chronic pancreatitis is also a risk factor for pancreatic cancer, though the estimated risk varies significantly among studies. For instance, a prospective study from France showed a relative risk of 19.0 among patients with chronic pancreatitis [233], whereas a 10-year case-control study in Italy projected a relative risk of 5.7 among chronic pancreatitis patients [234]. The risk factors in those with chronic pancreatitis and mechanisms by which chronic inflammation transitions into invasive cancer are still being clarified. Risk factors for chronic pancreatitis include toxic-metabolic factors such as heavy alcohol use, tobacco use, hypercalcemia, and chronic renal insufficiency; genetic factors such as hereditary pancreatitis; autoimmune factors such as isolated autoimmune chronic pancreatitis; recurrent and severe acute pancreatitis including post-radiation exposure and vascular disease; obstructive factors such as with duct obstructions from tumors or trauma; and idiopathic.

Individuals with neoplastic pancreatic cysts, specifically mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasm (IPMN), are at risk of developing pancreatic adenocarcinoma from malignant degeneration of the cyst as well as de novo pancreatic cancer not directly associated with the cystic lesion. The increased use of cross-sectional imaging has resulted in a much higher prevalence of pancreatic cysts than previously known, and many of those cysts are mucinous ones (MCNs or IPMNs), which carry a premalignant potential. Pancreatic cyst features that increase malignant risk include size greater or equal to 3 cm, presence of a solid component of the cyst, as well as a dilated main pancreatic duct [235]. The best evidence at this time suggests that individuals with two or more of these high-risk features should be evaluated with endoscopic ultrasound (EUS) with fine needle aspiration (FNA) of the cyst for cytological and biochemical analysis.

Environmental and host risk factors for pancreatic cancer include cigarette smoking, obesity, diet, and physical inactivity. Cigarette smoking has been shown to be a strong risk factor for pancreatic cancer with a large prospective study reporting a relative risk among current smokers of 2.5 [236]. As expected, the duration of smoking appears to be directly correlated with risk, as those who have a 40-year pack history carry a 3- to 5-fold increased risk [237]. Early-onset diabetes mellitus also appears to be associated with pancreatic cancer as approximately 80% have either diabetes or impaired glucose tolerance upon diagnosis [238]. It is unclear at this time whether diabetes predisposes to pancreatic cancer or if the cancer itself promotes the development of diabetes [239]. In addition, obesity has been shown in several studies to be associated with the development of pancreatic cancer. Results from the Health Professionals Follow-Up Study and the Nurses' Health Study showed that a body mass index (BMI) greater than 30 kg/m^2 was associated with a relative risk of 1.72 [240]. Taller height also appeared to be further associated with an increased risk of pancreatic cancer with a relative risk of 1.81 [240]. Physical activity appeared to have a protective effect. Moderate amounts of physical activity, particularly in those who were overweight or obese, carried a reduced risk of pancreatic cancer with a relative risk of 0.45 [240]. Dietary intake of large amounts of saturated fat and meat have been associated with pancreatic cancer in most but not all studies [237, 241], while diets high in fruits and vegetables have been shown to be protective in case-control but not in prospective studies [242, 243]. Occupational exposures, such as chlorinated and polycyclic aromatic hydrocarbons, may also increase the risk of pancreatic cancer [244, 245].

Screening

Although there have been innovations in the treatment of pancreatic cancer, diagnosing pancreatic cancer in its potentially curative stages remains challenging. Screening modalities for pancreatic cancer include imaging such as computed tomography (CT), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP); endoscopic procedures such as endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP); and tumor markers such as CA 19-9. Molecular-based genetic markers are on the horizon but not yet used in clinical practice. Despite the variety of screening modalities available, the optimal approach remains unclear. CT scan is a noninvasive and readily available imaging tool, but is the least sensitive of all screening modalities, especially if the pancreatic duct is not dilated [246]. It is also associated with a significant amount of radiation, especially if repeated over years for surveillance. MRI with MRCP, however, may currently be the preferred imaging tool as it is noninvasive, is not associated with radiation exposure or procedural complications, and has equal (or even greater) diagnostic accuracy for IPMN when compared to CT scan or ERCP [247, 248]. Although only performed at a few centers, secretin-enhanced MRCP is an excellent way to assess for small duct lesions. EUS is an excellent endoscopic modality [249] to screen for pancreatic cancer and pancreatic intraepithelial neoplasia (PanIN) and also can detect mural nodules within IPMNs, which may predict malignant transformation of those cysts. Disadvantages of EUS include its cost, procedural complications, decreased sensitivity in those with chronic pancreatitis, and interobserver variability. ERCP is another endoscopic modality, but its use as a screening test is limited due to the risk of complications [247]. Serum markers such as CA 19-9 have been used, but currently are not recommended for screening purposes due to suboptimal sensitivity and specificity and only should be employed to risk stratify patients prior to treatment and as part of a posttreatment surveillance protocol [250]. There are also multiple molecular-based tests using DNA microarray technology as well as biomarkers on the horizon, but utility of these in screening and surveillance of pancreatic cancer is not yet substantiated [251].

Evidence for Screening

At present, only approximately 10–20% of patients diagnosed with pancreatic cancer are operative candidates, which is currently the only potentially curative treatment [252]. However, despite this, only approximately 15% of those undergoing surgery survive past 2 years. The goal of screening is, therefore, to identify pancreatic malignancies at earlier, more operable, and hence more curable stages. However, routine screening has been limited in the average-risk population by the low incidence of pancreatic cancer, the cost of screening, and the suboptimal sensitivity and specificity of many screening modalities and from morbidity of endoscopic screening strategies. Despite this, some advocate screening in high-risk populations in order to identify noninvasive neoplasia including intraductal papillary mucinous neoplasm (IPMN) and high-grade pancreatic intraepithelial neoplasia (PanIN). There have been few prospective studies to date that have evaluated screening of high-risk individuals [251].

In support of screening high-risk individuals, Brentnall et al. evaluated ERCP, EUS, CT scan, and tumor markers including carcinoembryonic antigen (CEA) and CA 19-9 in patients with a familial clustering of pancreatic cancer consisting of two or more relatives with pancreatic cancer spanning two or more generations [219]. Out of 14 patients, 7 had abnormal findings and all underwent surgery with PanIN found on histologic assessment. In addition, a prospective study completed by the American Cancer of the

Pancreas Screening (CAPS) Consortium studied 225 high-risk individuals who were asymptomatic and underwent a single screening with CT, MRI, or EUS [253]. Forty-two percent were found to have abnormalities consisting of a pancreatic lesion or dilated duct with the majority found to have IPMNs [253]. EUS was found to be the most sensitive test, detecting an abnormality in 42.6% of individuals, while MRI and CT scan detected abnormalities in 33% and 11%, respectively [253].

Guidelines

Given the low prevalence of pancreatic cancer, the lack of accurate noninvasive testing modalities, and the absence of evidence that screening improves survival, there are no recommendations from any major societies for screening of asymptomatic average-risk individuals for pancreatic cancer. The US Preventive Services Task Force recommends against screening for pancreatic cancer in asymptomatic adults [254]. Screening of high-risk individuals remains controversial and is currently only supported by one guideline written by a consensus committee of the European Registry of Hereditary Pancreatic Diseases, Midwest Multi-Center Pancreatic Study Group, and International Association of Pancreatology. They recommend screening only in individuals with hereditary pancreatitis at age 40 or greater [226], while in 2012, an International Cancer of the Pancreas (CAPS) Consortium recommended screening with EUS or MRCP in all individuals with a >10-fold increased risk of pancreatic cancer [255]. These individuals would include not only those with hereditary pancreatitis but also Peutz-Jeghers syndrome; those with one or more first- or second-degree relatives with pancreatic cancer and who also carry a mutation such as BRCA1, BRCA2, or p16 or who have been diagnosed with Lynch syndrome; or those with three or more first-, second-, or third-degree relatives with pancreatic cancer, with at least one who is a first-degree relative [256]. Screening can also be considered in those individuals who have two first-degree relatives with pancreatic cancer [256]. However, both the National Comprehensive Cancer Network (NCCN) and the American Gastroenterological Association (AGA) do not recommend any screening even for high-risk individuals, as screening has not been shown to improve survival [257]. A more recent prospective study from three expert European centers showed that the benefits of surveillance in patients with a history of family pancreatic cancer are inconclusive [258]. In terms of screening options, there is no consensus on the best modality to use, on the timing of when to initiate screening, on the appropriate screening interval, or on the optimal management of those with lesions detected through these screening modalities.

Conclusion

In conclusion, the role of screening in gastrointestinal malignancies varies depending on the prevalence of the disease as well as the cost and benefit of screening. Colorectal cancer screening, using one of several methods, is broadly recommended for the general population, while screening for hepatocellular carcinoma and esophageal cancer is only recommended for those with established risk factors (hepatitis B and cirrhosis, and Barrett's esophagus, respectively). Screening for stomach cancer and pancreatic cancer is not recommended at this time. Research is ongoing for accurate noninvasive screening tests for many of these diseases and will hopefully lead to more options for the early detection and treatment of these common malignant conditions.

Acknowledgments *Disclaimer*: The content does not represent the views of the Department of Veterans Affairs or the US government.

Disclosure Statement: None of the authors have any commercial association that might represent a conflict of interest in relation to the submitted manuscript.

References

1. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO; 1968. Available from: http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
3. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? Cancer Epidemiol Biomark Prev. 2010;19(6):1468–70.
4. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. Br J Cancer. 2009;101(5):855–9.
5. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
6. Pandeya N, Williams G, Green AC, Webb PM, Whiteman DC, Australian Cancer S. Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. Gastroenterology. 2009;136(4):1215–24, e1–2.
7. Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer. 2005;113(3):456–63.
8. Lu SH, Montesano R, Zhang MS, Feng L, Luo FJ, Chui SX, et al. Relevance of N-nitrosamines to esophageal cancer in China. J Cell Physiol Suppl. 1986;4:51–8.
9. Islami F, Ren JS, Taylor PR, Kamangar F. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. Br J Cancer. 2009;101(9):1641–7.
10. Chang-Claude J, Becher H, Blettner M, Qiu S, Yang G, Wahrendorf J. Familial aggregation of oesophageal cancer in a high incidence area in China. Int J Epidemiol. 1997;26(6):1159–65.
11. Gammon MD, Schoenberg JB, Ahsan H, Risch HA, Vaughan TL, Chow WH, et al. Tobacco, alcohol, and socioeconomic status

and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst. 1997;89(17):1277–84.
12. Islami F, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Abedi-Ardekani B, et al. Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. Int J Epidemiol. 2009;38(4):978–88.
13. Petit T, Georges C, Jung GM, Borel C, Bronner G, Flesch H, et al. Systematic esophageal endoscopy screening in patients previously treated for head and neck squamous-cell carcinoma. Ann Oncol. 2001;12(5):643–6.
14. Das A, Thomas S, Zablotska LB, Neugut AI, Chak A. Association of esophageal adenocarcinoma with other subsequent primary cancers. J Clin Gastroenterol. 2006;40(5):405–11.
15. Iwaya T, Maesawa C, Ogasawara S, Tamura G. Tylosis esophageal cancer locus on chromosome 17q25.1 is commonly deleted in sporadic human esophageal cancer. Gastroenterology. 1998;114(6):1206–10.
16. Stevens HP, Kelsell DP, Bryant SP, Bishop DT, Spurr NK, Weissenbach J, et al. Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. Literature survey and proposed updated classification of the keratodermas. Arch Dermatol. 1996;132(6):640–51.
17. Sandler RS, Nyren O, Ekbom A, Eisen GM, Yuen J, Josefsson S. The risk of esophageal cancer in patients with achalasia. A population-based study. JAMA. 1995;274(17):1359–62.
18. Appelqvist P, Salmo M. Lye corrosion carcinoma of the esophagus: a review of 63 cases. Cancer. 1980;45(10):2655–8.
19. Campos GM, DeMeester SR, Peters JH, Oberg S, Crookes PF, Hagen JA, et al. Predictive factors of Barrett esophagus: multivariate analysis of 502 patients with gastroesophageal reflux disease. Arch Surg. 2001;136(11):1267–73.
20. Abrams JA, Fields S, Lightdale CJ, Neugut AI. Racial and ethnic disparities in the prevalence of Barrett's esophagus among patients who undergo upper endoscopy. Clin Gastroenterol Hepatol. 2008;6(1):30–4.
21. Edelstein ZR, Bronner MP, Rosen SN, Vaughan TL. Risk factors for Barrett's esophagus among patients with gastroesophageal reflux disease: a community clinic-based case-control study. Am J Gastroenterol. 2009;104(4):834–42.
22. Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, Vaughan TL. Central adiposity and risk of Barrett's esophagus. Gastroenterology. 2007;133(2):403–11.
23. Chak A, Ochs-Balcom H, Falk G, Grady WM, Kinnard M, Willis JE, et al. Familiality in Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction. Cancer Epidemiol Biomark Prev. 2006;15(9):1668–73.
24. Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based practice. GORGE consortium. Gastroenterology Outcomes Research Group in Endoscopy. Am J Gastroenterol. 1997;92(8):1293–7.
25. Eisen GM, Sandler RS, Murray S, Gottfried M. The relationship between gastroesophageal reflux disease and its complications with Barrett's esophagus. Am J Gastroenterol. 1997;92(1):27–31.
26. Desai TK, Krishnan K, Samala N, Singh J, Cluley J, Perla S, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut. 2012;61(7):970–6.
27. Wani S, Falk G, Hall M, Gaddam S, Wang A, Gupta N, et al. Patients with nondysplastic Barrett's esophagus have low risks for developing dysplasia or esophageal adenocarcinoma. Clin Gastroenterol Hepatol. 2011;9(3):220–7; quiz e26.
28. Srivastava A, Hornick JL, Li X, Blount PL, Sanchez CA, Cowan DS, et al. Extent of low-grade dysplasia is a risk factor for the development of esophageal adenocarcinoma in Barrett's esophagus. Am J Gastroenterol. 2007;102(3):483–93; quiz 694.
29. Wani S, Falk GW, Post J, Yerian L, Hall M, Wang A, et al. Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. Gastroenterology. 2011;141(4):1179–86, 86 e1.
30. de Jonge PJ, van Blankenstein M, Looman CW, Casparie MK, Meijer GA, Kuipers EJ. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study. Gut. 2010;59(8):1030–6.
31. Qiao Y, Hyder A, Bae SJ, Zarin W, O'Neill TJ, Marcon NE, et al. Surveillance in patients with Barrett's esophagus for early detection of esophageal adenocarcinoma: a systematic review and meta-analysis. Clin Transl Gastroenterol. 2015;6:e131.
32. Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. Gastroenterology. 2002;122(3):633–40.
33. Wong T, Tian J, Nagar AB. Barrett's surveillance identifies patients with early esophageal adenocarcinoma. Am J Med. 2010;123(5):462–7.
34. Verbeek RE, Leenders M, Ten Kate FJ, van Hillegersberg R, Vleggaar FP, van Baal JW, et al. Surveillance of Barrett's esophagus and mortality from esophageal adenocarcinoma: a population-based cohort study. Am J Gastroenterol. 2014;109(8):1215–22.
35. Bhat SK, McManus DT, Coleman HG, Johnston BT, Cardwell CR, McMenamin U, et al. Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study. Gut. 2015;64(1):20–5.
36. Levine DS, Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. Gastroenterology. 1993;105(1):40–50.
37. ASGE Standards of Practice Committee, Evans JA, Early DS, Fukami N, Ben-Menachem T, Chandrasekhara V, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc. 2012;76(6):1087–94.
38. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011;140(3):1084–91.
39. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG Clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1):30–50; quiz 1.
40. Montgomery E, Bronner MP, Goldblum JR, Greenson JK, Haber MM, Hart J, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol. 2001;32(4):368–78.
41. Reid BJ, Haggitt RC, Rubin CE, Roth G, Surawicz CM, Van Belle G, et al. Observer variation in the diagnosis of dysplasia in Barrett's esophagus. Hum Pathol. 1988;19(2):166–78.
42. Sharma P. Low-grade dysplasia in Barrett's esophagus. Gastroenterology. 2004;127(4):1233–8.
43. Sharma P, Wani S, Rastogi A, Bansal A, Higbee A, Mathur S, et al. The diagnostic accuracy of esophageal capsule endoscopy in patients with gastroesophageal reflux disease and Barrett's esophagus: a blinded, prospective study. Am J Gastroenterol. 2008;103(3):525–32.
44. Jobe BA, Hunter JG, Chang EY, Kim CY, Eisen GM, Robinson JD, et al. Office-based unsedated small-caliber endoscopy is equivalent to conventional sedated endoscopy in screening and surveillance for Barrett's esophagus: a randomized and blinded comparison. Am J Gastroenterol. 2006;101(12):2693–703.
45. Kadri SR, Lao-Sirieix P, O'Donovan M, Debiram I, Das M, Blazeby JM, et al. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. BMJ. 2010;341:c4372.
46. Haughey BH, Gates GA, Arfken CL, Harvey J. Meta-analysis of second malignant tumors in head and neck cancer: the case for

an endoscopic screening protocol. Ann Otol Rhinol Laryngol. 1992;101(2 Pt 1):105–12.
47. Hirota WK, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointest Endosc. 2006;63(4):570–80.
48. Rodriguez S, Mattek N, Lieberman D, Fennerty B, Eisen G. Barrett's esophagus on repeat endoscopy: should we look more than once? Am J Gastroenterol. 2008;103(8):1892–7.
49. Streitz JM Jr, Andrews CW Jr, Ellis FH Jr. Endoscopic surveillance of Barrett's esophagus. Does it help? J Thorac Cardiovasc Surg. 1993;105(3):383–7; discussion 7–8.
50. Peters JH, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. J Thorac Cardiovasc Surg. 1994;108(5):813–21; discussion 21–2.
51. Corley DA, Mehtani K, Quesenberry C, Zhao W, de Boer J, Weiss NS. Impact of endoscopic surveillance on mortality from Barrett's esophagus-associated esophageal adenocarcinomas. Gastroenterology. 2013;145(2):312–9 e1.
52. Old O, Moayyedi P, Love S, Roberts C, Hapeshi J, Foy C, et al. Barrett's Oesophagus Surveillance versus endoscopy at need Study (BOSS): protocol and analysis plan for a multicentre randomized controlled trial. J Med Screen. 2015;22(3):158–64.
53. Isobe Y, Nashimoto A, Akazawa K, Oda I, Hayashi K, Miyashiro I, et al. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. Gastric Cancer. 2011;14(4):301–16.
54. Cunningham SC, Kamangar F, Kim MP, Hammoud S, Haque R, Maitra A, et al. Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution. J Gastrointest Surg. 2005;9(5):718–25.
55. Marugame T, Dongmei Q. Comparison of time trends in stomach cancer incidence (1973–1997) in East Asia, Europe and USA, from cancer incidence in five continents Vol. IV–VIII. Jpn J Clin Oncol. 2007;37(3):242–3.
56. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med. 2001;345(11):784–9.
57. Schistosomes, liver flukes and Helicobacter pylori. Lyon: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; 1994. IARC Monogr Eval Carcinog Risks Hum. 1994;61:1–241.
58. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607–15.
59. Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, et al. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology. 2016;150(5):1113–24 e5.
60. Leung WK, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, et al. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncol. 2008;9(3):279–87.
61. Miwa H, Go MF, Sato N. H. Pylori and gastric cancer: the Asian enigma. Am J Gastroenterol. 2002;97(5):1106–12.
62. The EUROGAST Study Group. An international association between Helicobacter pylori infection and gastric cancer. Lancet. 1993;341(8857):1359–62.
63. Capelle LG, Van Grieken NC, Lingsma HF, Steyerberg EW, Klokman WJ, Bruno MJ, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology. 2010;138(2):487–92.
64. Park SY, Ryu JK, Park JH, Yoon H, Kim JY, Yoon YB, et al. Prevalence of gastric and duodenal polyps and risk factors for duodenal neoplasm in Korean patients with familial adenomatous polyposis. Gut Liver. 2011;5(1):46–51.
65. Lynch HT, Snyder C, Davies JM, Lanspa S, Lynch J, Gatalica Z, et al. FAP, gastric cancer, and genetic counseling featuring children and young adults: a family study and review. Familial Cancer. 2010;9(4):581–8.
66. van Lier MG, Westerman AM, Wagner A, Looman CW, Wilson JH, de Rooij FW, et al. High cancer risk and increased mortality in patients with Peutz-Jeghers syndrome. Gut. 2011;60(2):141–7.
67. Masciari S, Dewanwala A, Stoffel EM, Lauwers GY, Zheng H, Achatz MI, et al. Gastric cancer in individuals with Li-Fraumeni syndrome. Genet Med. 2011;13(7):651–7.
68. Stanich PP, Francis DL, Sweetser S. The spectrum of findings in Cowden syndrome. Clin Gastroenterol Hepatol. 2011;9(1):e2–3.
69. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
70. Correa P. The biological model of gastric carcinogenesis. IARC Sci Publ. 2004;157:301–10.
71. Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: a state of the art review. Gastroenterol Hepatol Bed Bench. 2015;8(Suppl 1):S6–S14.
72. de Vries AC, van Grieken NC, Looman CW, Casparie MK, de Vries E, Meijer GA, et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. Gastroenterology. 2008;134(4):945–52.
73. Jass JR, Filipe MI. The mucin profiles of normal gastric mucosa, intestinal metaplasia and its variants and gastric carcinoma. Histochem J. 1981;13(6):931–9.
74. Akiyama J, Uemura N. Intestinal metaplasia subtype and gastric cancer risk. J Gastroenterol Hepatol. 2009;24(1):4–6.
75. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy. 2012;44(1):74–94.
76. Gomez JM, Wang AY. Gastric intestinal metaplasia and early gastric cancer in the west: a changing paradigm. Gastroenterol Hepatol (NY). 2014;10(6):369–78.
77. ASGE Standards of Practice Committee, Evans JA, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc. 2015;82(1):1–8.
78. Rugge M, Cassaro M, Di Mario F, Leo G, Leandro G, Russo VM, et al. The long term outcome of gastric non-invasive neoplasia. Gut. 2003;52(8):1111–6.
79. Rugge M, Farinati F, Baffa R, Sonego F, Di Mario F, Leandro G, et al. Gastric epithelial dysplasia in the natural history of gastric cancer: a multicenter prospective follow-up study. Interdisciplinary Group on Gastric Epithelial Dysplasia. Gastroenterology. 1994;107(5):1288–96.
80. Fennerty MB. Gastric intestinal metaplasia on routine endoscopic biopsy. Gastroenterology. 2003;125(2):586–90.
81. Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, et al. E-cadherin germline mutations in familial gastric cancer. Nature. 1998;392(6674):402–5.
82. Caron O, Schielke A, Svrcek M, Flejou JF, Garzon J, Olschwang S, et al. Usefulness of prophylactic gastrectomy in a novel large hereditary diffuse gastric cancer (HDGC) family. Am J Gastroenterol. 2008;103(8):2160–1.
83. Murphy G, Dawsey SM, Engels EA, Ricker W, Parsons R, Etemadi A, et al. Cancer risk after pernicious anemia in the US elderly population. Clin Gastroenterol Hepatol. 2015;13(13):2282–9 e1–4.

84. Oshima A, Hirata N, Ubukata T, Umeda K, Fujimoto I. Evaluation of a mass screening program for stomach cancer with a case-control study design. Int J Cancer. 1986;38(6):829–33.
85. Fukao A, Tsubono Y, Tsuji I, Hisamichi S, Sugahara N, Takano A. The evaluation of screening for gastric cancer in Miyagi prefecture, Japan: a population-based case-control study. Int J Cancer. 1995;60(1):45–8.
86. Abe Y, Mitsushima T, Nagatani K, Ikuma H, Minamihara Y. Epidemiological evaluation of the protective effect for dying of stomach cancer by screening programme for stomach cancer with applying a method of case-control study--a study of an efficient screening programme for stomach cancer. Nihon Shokakibyo Gakkai Zasshi. 1995;92(5):836–45.
87. Tsubono Y, Hisamichi S. Screening for gastric cancer in Japan. Gastric Cancer. 2000;3(1):9–18.
88. Pisani P, Oliver WE, Parkin DM, Alvarez N, Vivas J. Case-control study of gastric cancer screening in Venezuela. Br J Cancer. 1994;69(6):1102–5.
89. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol. 2008;38(4):259–67.
90. Hamashima C, Ogoshi K, Okamoto M, Shabana M, Kishimoto T, Fukao A. A community-based, case-control study evaluating mortality reduction from gastric cancer by endoscopic screening in Japan. PLoS One. 2013;8(11):e79088.
91. Choi KS, Jun JK, Park EC, Park S, Jung KW, Han MA, et al. Performance of different gastric cancer screening methods in Korea: a population-based study. PLoS One. 2012;7(11):e50041.
92. Hamashima C, Shabana M, Okada K, Okamoto M, Osaki Y. Mortality reduction from gastric cancer by endoscopic and radiographic screening. Cancer Sci. 2015;106(12):1744–9.
93. Dinis-Ribeiro M, Yamaki G, Miki K, Costa-Pereira A, Matsukawa M, Kurihara M. Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. J Med Screen. 2004;11(3):141–7.
94. Sugano K. Screening of gastric cancer in Asia. Best Pract Res Clin Gastroenterol. 2015;29(6):895–905.
95. ASGE Standards of Practice Committee, Wang A, Shaukat A, Acosta RD, Bruining DH, Chandrasekhara V, et al. Race and ethnicity considerations in GI endoscopy. Gastrointest Endosc. 2015;82(4):593–9.
96. Kim Y, Jun JK, Choi KS, Lee HY, Park EC. Overview of the National Cancer screening programme and the cancer screening status in Korea. Asian Pac J Cancer Prev. 2011;12(3):725–30.
97. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759–67.
98. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525–32.
99. Roy HK, Bianchi LK. Moving toward personalization of colorectal cancer screening: comment on "influence of race and sex on prevalence and recurrence of colon polyps". Arch Intern Med. 2010;170(13):1132–4.
100. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol. 2001;96(10):2992–3003.
101. Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. J Natl Cancer Inst. 1998;90(14):1039–71.
102. Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med. 2006;355(18):1863–72.
103. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. Gut. 2007;56(11):1585–9.
104. Hoffmeister M, Schmitz S, Karmrodt E, Stegmaier C, Haug U, Arndt V, et al. Male sex and smoking have a larger impact on the prevalence of colorectal neoplasia than family history of colorectal cancer. Clin Gastroenterol Hepatol. 2010;8(10):870–6.
105. Young TB, Wolf DA. Case-control study of proximal and distal colon cancer and diet in Wisconsin. Int J Cancer. 1988;42(2):167–75.
106. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst. 2009;101(4):256–66.
107. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med. 2006;355(9):873–84.
108. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med. 2006;355(9):885–95.
109. Grodstein F, Martinez ME, Platz EA, Giovannucci E, Colditz GA, Kautzky M, et al. Postmenopausal hormone use and risk for colorectal cancer and adenoma. Ann Intern Med. 1998;128(9):705–12.
110. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010;138(6):2029–43 e10.
111. Raj KP, Taylor TH, Wray C, Stamos MJ, Zell JA. Risk of second primary colorectal cancer among colorectal cancer cases: a population-based analysis. J Carcinog. 2011;10:6.
112. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med. 1992;326(10):658–62.
113. Rhodes JM, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. Trends Mol Med. 2002;8(1):10–6.
114. Bernstein CN, Kraut A, Blanchard JF, Rawsthorne P, Yu N, Walld R. The relationship between inflammatory bowel disease and socioeconomic variables. Am J Gastroenterol. 2001;96(7):2117–25.
115. Feagins LA, Souza RF, Spechler SJ. Carcinogenesis in IBD: potential targets for the prevention of colorectal cancer. Nat Rev Gastroenterol Hepatol. 2009;6(5):297–305.
116. Petersen GM, Slack J, Nakamura Y. Screening guidelines and premorbid diagnosis of familial adenomatous polyposis using linkage. Gastroenterology. 1991;100(6):1658–64.
117. Bisgaard ML, Bulow S. Familial adenomatous polyposis (FAP): genotype correlation to FAP phenotype with osteomas and sebaceous cysts. Am J Med Genet A. 2006;140(3):200–4.
118. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329(27):1977–81.
119. Muller AD, Sonnenberg A. Protection by endoscopy against death from colorectal cancer. A case-control study among veterans. Arch Intern Med. 1995;155(16):1741–8.
120. Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med. 1995;123(12):904–10.
121. Lin OS, Kozarek RA, Cha JM. Impact of sigmoidoscopy and colonoscopy on colorectal cancer incidence and mortality: an evidence-based review of published prospective and retrospective studies. Intest Res. 2014;12(4):268–74.
122. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med. 2009;150(1):1–8.
123. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality

after colonoscopy varies by site of the cancer. Gastroenterology. 2010;139(4):1128–37.
124. Manser CN, Bachmann LM, Brunner J, Hunold F, Bauerfeind P, Marbet UA. Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: a closed cohort study. Gastrointest Endosc. 2012;76(1):110–7.
125. Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369(12):1095–105.
126. Kahi CJ, Imperiale TF, Juliar BE, Rex DK. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clin Gastroenterol Hepatol. 2009;7(7):770–5; quiz 11.
127. Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst. 2010;102(2):89–95.
128. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med. 2011;154(1):22–30.
129. Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M, Italian Multicentre Study G. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut. 2001;48(6):812–5.
130. Lohsiriwat V. Colonoscopic perforation: incidence, risk factors, management and outcome. World J Gastroenterol: WJG. 2010;16(4):425–30.
131. Rosenthal E. The $2.7 trillion medical bill. Colonoscopies explain why U.S. leads the world in health expenditures. New York Times. June 1, 2013.
132. Warren JL, Klabunde CN, Mariotto AB, Meekins A, Topor M, Brown ML, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med. 2009;150(12):849–57, W152.
133. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143(3):844–57.
134. Selby JV, Friedman GD, Collen MF. Sigmoidoscopy and mortality from colorectal cancer: the Kaiser Permanente Multiphasic Evaluation Study. J Clin Epidemiol. 1988;41(5):427–34.
135. Kavanagh AM, Giovannucci EL, Fuchs CS, Colditz GA. Screening endoscopy and risk of colorectal cancer in United States men. Cancer Causes Control. 1998;9(4):455–62.
136. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol. 1999;34(4):414–20.
137. Hoff G, Grotmol T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ. 2009;338:b1846.
138. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375(9726):1624–33.
139. Segnan N, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst. 2011;103(17):1310–22.
140. Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012;366(25):2345–57.
141. Klabunde CN, Lanier D, Nadel MR, McLeod C, Yuan G, Vernon SW. Colorectal cancer screening by primary care physicians: recommendations and practices, 2006–2007. Am J Prev Med. 2009;37(1):8–16.
142. Subramanian S, Amonkar MM, Hunt TL. Use of colonoscopy for colorectal cancer screening: evidence from the 2000 National Health Interview Survey. Cancer Epidemiol Biomark Prev. 2005;14(2):409–16.
143. Klabunde CN, Cronin KA, Breen N, Waldron WR, Ambs AH, Nadel MR. Trends in colorectal cancer test use among vulnerable populations in the United States. Cancer Epidemiol Biomark Prev. 2011;20(8):1611–21.
144. Burt RW, Barthel JS, Dunn KB, David DS, Drelichman E, Ford JM, et al. NCCN clinical practice guidelines in oncology. Colorectal cancer screening. J Natl Compr Cancer Netw. 2010;8(1):8–61.
145. Kim DH, Pickhardt PJ, Taylor AJ, Menias CO. Imaging evaluation of complications at optical colonoscopy. Curr Probl Diagn Radiol. 2008;37(4):165–77.
146. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149(9):638–58.
147. Zalis ME, Blake MA, Cai W, Hahn PF, Halpern EF, Kazam IG, et al. Diagnostic accuracy of laxative-free computed tomographic colonography for detection of adenomatous polyps in asymptomatic adults: a prospective evaluation. Ann Intern Med. 2012;156(10):692–702.
148. Zhu MM, Xu XT, Nie F, Tong JL, Xiao SD, Ran ZH. Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: a meta-analysis. J Dig Dis. 2010;11(3):148–60.
149. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328(19):1365–71.
150. Kewenter J, Brevinge H, Engaras B, Haglind E, Ahren C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. Scand J Gastroenterol. 1994;29(5):468–73.
151. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348(9040):1472–7.
152. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348(9040):1467–71.
153. Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013;369(12):1106–14.
154. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med. 2009;150(3):162–9.
155. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med. 2014;160(3):171.
156. Logan RF, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut. 2012;61(10):1439–46.
157. Imperiale TF, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;370(14):1287–97.
158. Palmqvist R, Engaras B, Lindmark G, Hallmans G, Tavelin B, Nilsson O, et al. Prediagnostic levels of carcinoembryonic antigen

and CA 242 in colorectal cancer: a matched case-control study. Dis Colon Rectum. 2003;46(11):1538–44.
159. Jin P, Kang Q, Wang X, Yang L, Yu Y, Li N, et al. Performance of a second generation methylated SEPT9 test in detecting colorectal neoplasm. J Gastroenterol Hepatol. 2015;30:830–3.
160. Pawa N, Arulampalam T, Norton JD. Screening for colorectal cancer: established and emerging modalities. Nat Rev Gastroenterol Hepatol. 2011;8(12):711–22.
161. Overholt BF, Wheeler DJ, Jordan T, Fritsche HA. CA11-19: a tumor marker for the detection of colorectal cancer. Gastrointest Endosc. 2016;83(3):545–51.
162. Inadomi JM, Vijan S, Janz NK, Fagerlin A, Thomas JP, Lin YV, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med. 2012;172(7):575–82.
163. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005;120(1):15–20.
164. Kanaan Z, Rai SN, Eichenberger MR, Roberts H, Keskey B, Pan J, et al. Plasma miR-21: a potential diagnostic marker of colorectal cancer. Ann Surg. 2012;256(3):544–51.
165. Luo X, Stock C, Burwinkel B, Brenner H. Identification and evaluation of plasma microRNAS for early detection of colorectal cancer. PLoS One. 2013;8(5):e62880.
166. Wang Q, Huang Z, Ni S, Xiao X, Xu Q, Wang L, et al. Plasma miR-601 and miR-760 are novel biomarkers for the early detection of colorectal cancer. PLoS One. 2012;7(9):e44398.
167. Giraldez MD, Lozano JJ, Ramirez G, Hijona E, Bujanda L, Castells A, et al. Circulating microRNAs as biomarkers of colorectal cancer: results from a genome-wide profiling and validation study. Clin Gastroenterol Hepatol. 2013;11(6):681–8 e3.
168. Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin. 2008;58(3):130–60.
169. Calonge N, Petitti DB, DeWitt TG, Dietrich AJ, Gregory KD, Harris R, Isham G, LeFevre ML, Leipzig RM, Loveland-Cherry C, Marion LN. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149(9):627–37.
170. Agrawal S, Bhupinderjit A, Bhutani MS, Boardman L, Nguyen C, Romero Y, et al. Colorectal cancer in African Americans. Am J Gastroenterol. 2005;100(3):515–23; discussion 4.
171. Kahi CJ, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, et al. Colonoscopy surveillance after colorectal cancer resection: recommendations of the US multi-society task force on colorectal cancer. Gastroenterology. 2016;150(3):758–68 e11.
172. Venook AP, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. Oncologist. 2010;15(Suppl 4):5–13.
173. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74–108.
174. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. Am J Gastroenterol. 2014;109(4):542–53.
175. Blonski W, Kotlyar DS, Forde KA. Non-viral causes of hepatocellular carcinoma. World J Gastroenterol: WJG. 2010;16(29):3603–15.
176. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127(5 Suppl 1):S35–50.
177. National Comprehensive Cancer Network. Hepatobiliary carcinoma (Version 1. 2016). Available from: http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed March 2016.
178. Lin OS, Keeffe EB, Sanders GD, Owens DK. Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. Aliment Pharmacol Ther. 2004;19(11):1159–72.
179. Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. Am J Gastroenterol. 2003;98(3):679–90.
180. Naimark D, Naglie G, Detsky AS. The meaning of life expectancy: what is a clinically significant gain? J Gen Intern Med. 1994;9(12):702–7.
181. Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–2.
182. Yang HI, Sherman M, Su J, Chen PJ, Liaw YF, Iloeje UH, et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Clin Oncol. 2010;28(14):2437–44.
183. Yuen MF, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol. 2009;50(1):80–8.
184. Chen JD, Yang HI, Iloeje UH, You SL, Lu SN, Wang LY, et al. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. Gastroenterology. 2010;138(5):1747–54.
185. Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther. 2008;28(9):1067–77.
186. Fattovich G, Giustina G, Sanchez-Tapias J, Quero C, Mas A, Olivotto PG, et al. Delayed clearance of serum HBsAg in compensated cirrhosis B: relation to interferon alpha therapy and disease prognosis. European Concerted Action on Viral Hepatitis (EUROHEP). Am J Gastroenterol. 1998;93(6):896–900.
187. Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology. 2009;136(1):138–48.
188. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53(3):726–36.
189. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25.
190. Tama M, Naylor P, Patel S, Altawil J, Gulati D, Antaki F, et al. Overestimate of fibrosis by FIBROSpect(R) II in African Americans complicates the management of their chronic hepatitis C. J Clin Transl Hepatol. 2016;4(1):12–9.
191. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. Ann Intern Med. 2013;159(5):372.
192. Patel K, Benhamou Y, Yoshida EM, Kaita KD, Zeuzem S, Torbenson M, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during albinterferon alfa-2b combination therapy for chronic hepatitis C. J Viral Hepat. 2009;16(3):178–86.
193. Patel K, Remlinger KS, Walker TG, Leitner P, Lucas JE, Gardner SD, et al. Multiplex protein analysis to determine fibrosis stage and progression in patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2014;12(12):2113–20 e1–3.
194. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. 2008;134(4):960–74.

195. Gobel T, Schadewaldt-Tummers J, Greiner L, Poremba C, Haussinger D, Erhardt A. Transient elastography improves detection of liver cirrhosis compared to routine screening tests. World J Gastroenterol: WJG. 2015;21(3):953–60.
196. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol. 2008;48(5):835–47.
197. Testino G, Leone S, Borro P. Alcohol and hepatocellular carcinoma: a review and a point of view. World J Gastroenterol: WJG. 2014;20(43):15943–54.
198. Schoniger-Hekele M, Muller C, Kutilek M, Oesterreicher C, Ferenci P, Gangl A. Hepatocellular carcinoma in Austria: aetiological and clinical characteristics at presentation. Eur J Gastroenterol Hepatol. 2000;12(8):941–8.
199. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. Ann Intern Med. 2012;156(12):841–7, W295.
200. Archambeaud I, Auble H, Nahon P, Planche L, Fallot G, Faroux R, et al. Risk factors for hepatocellular carcinoma in Caucasian patients with non-viral cirrhosis: the importance of prior obesity. Liver Int. 2015;35(7):1872–6.
201. Noureddin M, Rinella ME. Nonalcoholic fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. Clin Liver Dis. 2015;19(2):361–79.
202. Paul SB, Sreenivas V, Gamanagatti SR, Sharma H, Dhamija E, et al. Incidence and risk factors of hepatocellular carcinoma in patients with hepatic venous outflow tract obstruction. Aliment Pharmacol Ther. 2015;41(10):961–71.
203. Yeoman AD, Al-Chalabi T, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, et al. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: implications for follow-up and screening. Hepatology. 2008;48(3):863–70.
204. Daniele B, Bencivenga A, Megna AS, Tinessa V. Alpha-fetoprotein and ultrasonography screening for hepatocellular carcinoma. Gastroenterology. 2004;127(5 Suppl 1):S108–12.
205. Sherman M, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. Hepatology. 1995;22(2):432–8.
206. Lok AS, Sterling RK, Everhart JE, Wright EC, Hoefs JC, Di Bisceglie AM, et al. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. Gastroenterology. 2010;138(2):493–502.
207. Lok AS, Lai CL. Alpha-fetoprotein monitoring in Chinese patients with chronic hepatitis B virus infection: role in the early detection of hepatocellular carcinoma. Hepatology. 1989;9(1):110–5.
208. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther. 2009;30(1):37–47.
209. Pocha C, Dieperink E, McMaken KA, Knott A, Thuras P, Ho SB. Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography – a randomised study. Aliment Pharmacol Ther. 2013;38(3):303–12.
210. Wang JH, Chang KC, Kee KM, Chen PF, Yen YH, Tseng PL, et al. Hepatocellular carcinoma surveillance at 4- vs. 12-month intervals for patients with chronic viral hepatitis: a randomized study in community. Am J Gastroenterol. 2013;108(3):416–24.
211. Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology. 2011;54(6):1987–97.
212. Trevisani F, De Notariis S, Rapaccini G, Farinati F, Benvegnu L, Zoli M, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol. 2002;97(3):734–44.
213. Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol. 2010;53(2):291–7.
214. Pelletier SJ, Fu S, Thyagarajan V, Romero-Marrero C, Batheja MJ, Punch JD, et al. An intention-to-treat analysis of liver transplantation for hepatocellular carcinoma using organ procurement transplant network data. Liver Transpl. 2009;15(8):859–68.
215. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130(7):417–22.
216. Ries LA, Eisner MP, Kosary CL, et al. SEER cancer statistics review, 1973–1996. Bethesda: National Cancer Institute; 2000.
217. Levin B. An overview of preventive strategies for pancreatic cancer. Ann Oncol. 1999;10(Suppl 4):193–6.
218. Tersmette AC, Petersen GM, Offerhaus GJ, Falatko FC, Brune KA, Goggins M, et al. Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. Clin Cancer Res. 2001;7(3):738–44.
219. Brentnall TA. Management strategies for patients with hereditary pancreatic cancer. Curr Treat Options in Oncol. 2005;6(5):437–45.
220. Brune KA, Lau B, Palmisano E, Canto M, Goggins MG, Hruban RH, et al. Importance of age of onset in pancreatic cancer kindreds. J Natl Cancer Inst. 2010;102(2):119–26.
221. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res. 2004;64(7):2634–8.
222. Howes N, Greenhalf W, Neoptolemos J. Screening for early pancreatic ductal adenocarcinoma in hereditary pancreatitis. Med Clin North Am. 2000;84(3):719–38, xii.
223. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89(6):442–6.
224. Rebours V, Boutron-Ruault MC, Schnee M, Ferec C, Maire F, Hammel P, et al. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series. Am J Gastroenterol. 2008;103(1):111–9.
225. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA. 2001;286(2):169–70.
226. Ulrich CD, Consensus Committees of the European Registry of Hereditary Pancreatic Diseases. Pancreatic cancer in hereditary pancreatitis: consensus guidelines for prevention, screening and treatment. Pancreatology. 2001;1(5):416–22.
227. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447–53.
228. Swift M, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia-telangiectasia. N Engl J Med. 1991;325(26):1831–6.
229. Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009;302(16):1790–5.
230. Giardiello FM, Offerhaus GJ, Lee DH, Krush AJ, Tersmette AC, Booker SV, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. Gut. 1993;34(10):1394–6.
231. Sheldon CD, Hodson ME, Carpenter LM, Swerdlow AJ. A cohort study of cystic fibrosis and malignancy. Br J Cancer. 1993;68(5):1025–8.
232. Maisonneuve P, FitzSimmons SC, Neglia JP, Campbell PW 3rd, Lowenfels AB. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: a 10-year study. J Natl Cancer Inst. 2003;95(5):381–7.

233. Malka D, Hammel P, Maire F, Rufat P, Madeira I, Pessione F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. Gut. 2002;51(6):849–52.
234. Fernandez E, La Vecchia C, Porta M, Negri E, d'Avanzo B, Boyle P. Pancreatitis and the risk of pancreatic cancer. Pancreas. 1995;11(2):185–9.
235. Vege SS, Ziring B, Jain R, Moayyedi P, Clinical Guidelines C, American Gastroenterology A. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148(4):819–22; quize12–3.
236. Fuchs CS, Colditz GA, Stampfer MJ, Giovannucci EL, Hunter DJ, Rimm EB, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch Intern Med. 1996;156(19):2255–60.
237. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer. 2012;106(3):603–7.
238. Wang F, Herrington M, Larsson J, Permert J. The relationship between diabetes and pancreatic cancer. Mol Cancer. 2003;2:4.
239. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA. 1995;273(20):1605–9.
240. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA. 2001;286(8):921–9.
241. Thiebaut AC, Jiao L, Silverman DT, Cross AJ, Thompson FE, Subar AF, et al. Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. J Natl Cancer Inst. 2009;101(14):1001–11.
242. Norell SE, Ahlbom A, Erwald R, Jacobson G, Lindberg-Navier I, Olin R, et al. Diet and pancreatic cancer: a case-control study. Am J Epidemiol. 1986;124(6):894–902.
243. Howe GR, Jain M, Miller AB. Dietary factors and risk of pancreatic cancer: results of a Canadian population-based case-control study. Int J Cancer. 1990;45(4):604–8.
244. Ojajarvi A, Partanen T, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, et al. Risk of pancreatic cancer in workers exposed to chlorinated hydrocarbon solvents and related compounds: a meta-analysis. Am J Epidemiol. 2001;153(9):841–50.
245. Alguacil J, Porta M, Kauppinen T, Malats N, Kogevinas M, Carrato A, et al. Occupational exposure to dyes, metals, polycyclic aromatic hydrocarbons and other agents and K-ras activation in human exocrine pancreatic cancer. Int J Cancer. 2003;107(4):635–41.
246. Bronstein YL, Loyer EM, Kaur H, Choi H, David C, DuBrow RA, et al. Detection of small pancreatic tumors with multiphasic helical CT. AJR Am J Roentgenol. 2004;182(3):619–23.
247. Adamek HE, Albert J, Breer H, Weitz M, Schilling D, Riemann JF. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. Lancet. 2000;356(9225):190–3.
248. Albert J, Schilling D, Breer H, Jungius KP, Riemann JF, Adamek HE. Mucinous cystadenomas and intraductal papillary mucinous tumors of the pancreas in magnetic resonance cholangiopancreatography. Endoscopy. 2000;32(6):472–6.
249. Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. Ann Intern Med. 1999;131(4):247–55.
250. Frebourg T, Bercoff E, Manchon N, Senant J, Basuyau JP, Breton P, et al. The evaluation of CA 19-9 antigen level in the early detection of pancreatic cancer. A prospective study of 866 patients. Cancer. 1988;62(11):2287–90.
251. Greer JB, Whitcomb DC, Brand RE. Genetic predisposition to pancreatic cancer: a brief review. Am J Gastroenterol. 2007;102(11):2564–9.
252. Shaib Y, Davila J, Naumann C, El-Serag H. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. population-based study. Am J Gastroenterol. 2007;102(7):1377–82.
253. Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology. 2012;142(4):796–804; quiz e14–5.
254. Clinical Summary: Pancreatic Cancer: Screening. U.S. Preventive Services Task Force. April 2004. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/ClinicalSummaryFinal/pancreatic-cancer-screening. Accessed March 2016.
255. Brand RE, Lerch MM, Rubinstein WS, Neoptolemos JP, Whitcomb DC, Hruban RH, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut. 2007;56(10):1460–9.
256. Grover S, Syngal S. Hereditary pancreatic cancer. Gastroenterology. 2010;139(4):1076–80, 80 e1–2.
257. Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol. 2006;4(6):766–81; quiz 665.
258. Vasen H, Ibrahim I, Ponce CG, Slater EP, Matthai E, Carrato A, et al. Benefit of surveillance for pancreatic cancer in high-risk individuals: outcome of long-term prospective follow-up studies from three European expert centers. J Clin Oncol. 2016;34(17):2010–9.

Hereditary Gastrointestinal Cancers

33

Selvi Thirumurthi, Eduardo Vilar, and Patrick J. Lynch

Introduction

The main job of a medical oncologist is to confirm a cancer diagnosis, assure appropriate staging of the malignancy, and institute state-of-the-art treatment, typically chemotherapy for advanced disease or for adjuvant treatment for locally advanced tumors. Our mission in this chapter will be to highlight the intersection of these functions with the cancers that manifest an inherited susceptibility.

No more than about 3% to at most 5% of gastrointestinal (GI) malignancies show a clear inherited basis. As we shall see, there are only a few instances in which the presence of an underlying inherited susceptibility has an important bearing on prognosis or selection of chemotherapy. Nevertheless, the medical oncologist, as an institution's specialist in the area of cancer, will often be called upon to help develop and coordinate a program for the identification and management of inherited cancer susceptibility.

In this chapter, we will take a somewhat historical perspective and will combine broader issues of disease management with specific areas that selectively impact the medical oncologist. As will be seen, ongoing rapid advances in molecular technology are transforming the approach to personalized therapy in the cancer patient and to the diagnosis of underlying susceptibility. In our description of specific inherited syndromes, the focus will be the traditional one of recognizing characteristic disease expressions (phenotype) in the cancer patient, along with patterns of expression in families, the combination of which may suggest a very narrow range of conditions. Counseling regarding the advantages and limitations of mutation testing is followed by such testing. Detection of a pathogenic mutation may affect cancer care and survivorship surveillance, and direct predictive testing in at-risk relatives. While all of this may prove challenging to that majority of clinicians who do not work in the field of clinical cancer genetics, even this paradigm is being supplanted by the use of broader and more powerful germline genetic "panels." Panels are test arrays that can be readily ordered from a handful of clinical genetic testing laboratories and that offer identification of genetic susceptibility to colorectal cancer (CRC)/adenomas, breast cancer, endocrine neoplasia, and more. Other panels are not even limited to specific cancers. An entire body of literature is already developing to help guide the clinician through the range of options now available [1, 2]. The good news about panels is that the clinician needs to know very little about inherited cancer susceptibility in order to arrange testing that may provide a clear understanding of the basis for a patient's cancer risk. The bad news is that such testing, whether informative or not, typically opens up a host of issues that will likely need to be addressed by a team that does have expertise in the management of inherited cancer risk. Powerful tools carry powerful consequences when properly used and just as powerful consequences when misused.

Familial Adenomatous Polyposis

The first evidence that inherited susceptibility might contribute to the formation of precancerous adenomas and ultimately colorectal cancer involved familial adenomatous polyposis (FAP). Because of the very distinctive phenotype—the presence of hundreds to thousands of adenomas—the presence of such a disease phenotype clearly characterized the affected individual. As modern concepts of Mendelian inheritance evolved, it became obvious that FAP was an autosomal dominant condition. Until the discovery of the *APC* gene responsible for FAP, screening consisted of

S. Thirumurthi · P. J. Lynch (✉)
Department of Gastroenterology, Hepatology and Nutrition, University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: plynch@mdanderson.org

E. Vilar
Department of Clinical Cancer Prevention, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_33

sigmoidoscopy in the children of affected individuals. Upon recognition of polyps, the era of prophylactic surgery began, with the performance of colectomy (with ileo-rectal anastomosis or J-pouch reconstruction) or proctocolectomy with end-ileostomy. Thus, early on there was the potential to prevent malignancy by means of surveillance and early surgical intervention. Unfortunately, about 30% of cases of FAP present as de novo cases, with no obvious antecedent family history. Often such cases presented with symptoms of bleeding, anemia, or obstruction at an early age, and commonly with a delay in diagnosis and presence of advanced disease.

There is no evidence of a unique natural history, prognosis, or patterns of response to chemotherapy or radiation that differ in FAP compared with its sporadic counterparts.

Assuming a given patient is able to benefit from surgery and survives an initial colorectal cancer, he or she remains at risk of cancer of the remaining rectum. Also, the risk of duodenum cancer remains for colorectal cancer survivors and for those undergoing prophylactic colectomy. Tumors that arise in the GI tract following an initial colectomy or proctocolectomy are generally treated in the same fashion as such tumors occurring sporadically. However, an important consideration is the fact that about 10% of FAP patients and families carry a significant risk of intra-abdominal desmoid disease. Commonly, desmoids occur within several years of colectomy and may compromise attempts at further operation for new cancers in the rectum or upper GI tract. Desmoids are almost invariably benign, but their infiltrative pattern commonly causes obstruction of the bowel, ureters, or other vital structures. Their very unpredictable natural history makes prediction of response to intervention rather challenging. Some desmoids occur as single space-occupying masses in an old surgical wound and as such are often removed surgically. Ominously, however, desmoid disease is commonly an infiltrating ill-defined mass in the small bowel mesentery. Operations to resect such desmoids are commonly very bloody, involve sacrifice of small bowel leading to short gut, and may be followed by recurring desmoid in any event.

Despite the unpredictable natural history of desmoid tumors, attempts at medical management have been undertaken. Small and poorly controlled trials have employed agents such as sulindac, the common nonsteroidal anti-inflammatory drug (NSAID), and/or antiestrogen compounds tamoxifen and toremifene. When such agents are ineffective, then more aggressive chemotherapeutic measures may include use of doxorubicin (Adriamycin®). In some cases, a favorable response to chemotherapy can be followed by surgical resection. It has been our experience that even stable, relatively asymptomatic mesenteric desmoid disease can prevent completion of duodenectomy in patients with severe dysplasia or invasive cancer of the duodenum. At our institution, all patients with evidence of intra-abdominal desmoid related to FAP undergo consultation with a medical oncologist having a special expertise in soft-tissue sarcomas.

Depending on the institutional setting, an additional role for the medical oncologist can include oversight of surveillance programs for extraintestinal disease. Having a working knowledge of the tumor spectrum of FAP can be helpful in this regard (Fig. 33.1) [3]. Patients with FAP are at increased risk of thyroid cancer and brain tumors, primarily medulloblastoma. There is not a clear consensus regarding the role of thyroid screening in FAP. The available clinical practice guidelines such as those provided by the National Comprehensive Cancer Network (NCCN) in the USA (www.nccn.org) [4] or the European Society for Medical Oncology (ESMO) do provide some guidance in this area, in addition to providing a broad and at the same time detailed overview of management strategies for FAP (www.esmo.org) [5].

Aside from the immediate oncologic management of the patient with FAP are important issues having to do with predictive testing and coordination of surveillance. Not all patients with colon cancer and multiple polyps have an *APC* mutation. It is now clear that a similar phenotype can occur in patients with biallelic mutations in the *MUTYH* gene (so-called MYH-associated polyposis or MAP). This condition is autosomal recessive. Although siblings of affected patients are at 25% risk of being biallelic carriers themselves, and thus warrant surveillance, it is quite rare for a patient with a biallelic *MUTYH* mutation to have a clinically affected parent. Genetic counseling is thus very important as it has implications for risk to relatives. The benefits of testing are considerably different compared to FAP. Typically, a patient with MAP presents either with a colorectal cancer in the setting of oligopolyposis, or the patient may present with a polyposis phenotype at the time of a baseline screening colonoscopy. Data from Grover et al. have shown a near 90% likelihood of an *APC* mutation when a patient presents with a thousand or more adenomas. However, in patients with a modest number of adenomas (20–99), the likelihood of either an *APC* or *MUTYH* biallelic mutation is in the range of 3–5% [6]. A prior probability of 5% has commonly been taken as a threshold for consideration of mutational testing. Consequently, a patient with 20 or more adenomas, with or without cancer, may be considered an appropriate candidate for *APC* and *MUTYH* testing. If a diagnosis of MAP is made, it is now clear that such patients are at risk of upper GI malignancy—though it is not clear that an increased risk of desmoid disease is present in MAP. An ongoing controversy in MAP is the question of cancer risk in mono-allelic carriers. No clear guidelines exist for the screening of siblings and children who are carriers of one mutated allele. A common approach when counseling patients with biallelic *MUTYH* mutations is to do mutational testing on such a patient's spouse. If the spouse is free of an *MUTYH* mutation, then it can safely be concluded that all children will be mono-allelic carriers. A Spanish cohort study described *MUTYH* biallelic mutations in 7% of patients presenting with 10 or more colon polyps. The most frequent mutations

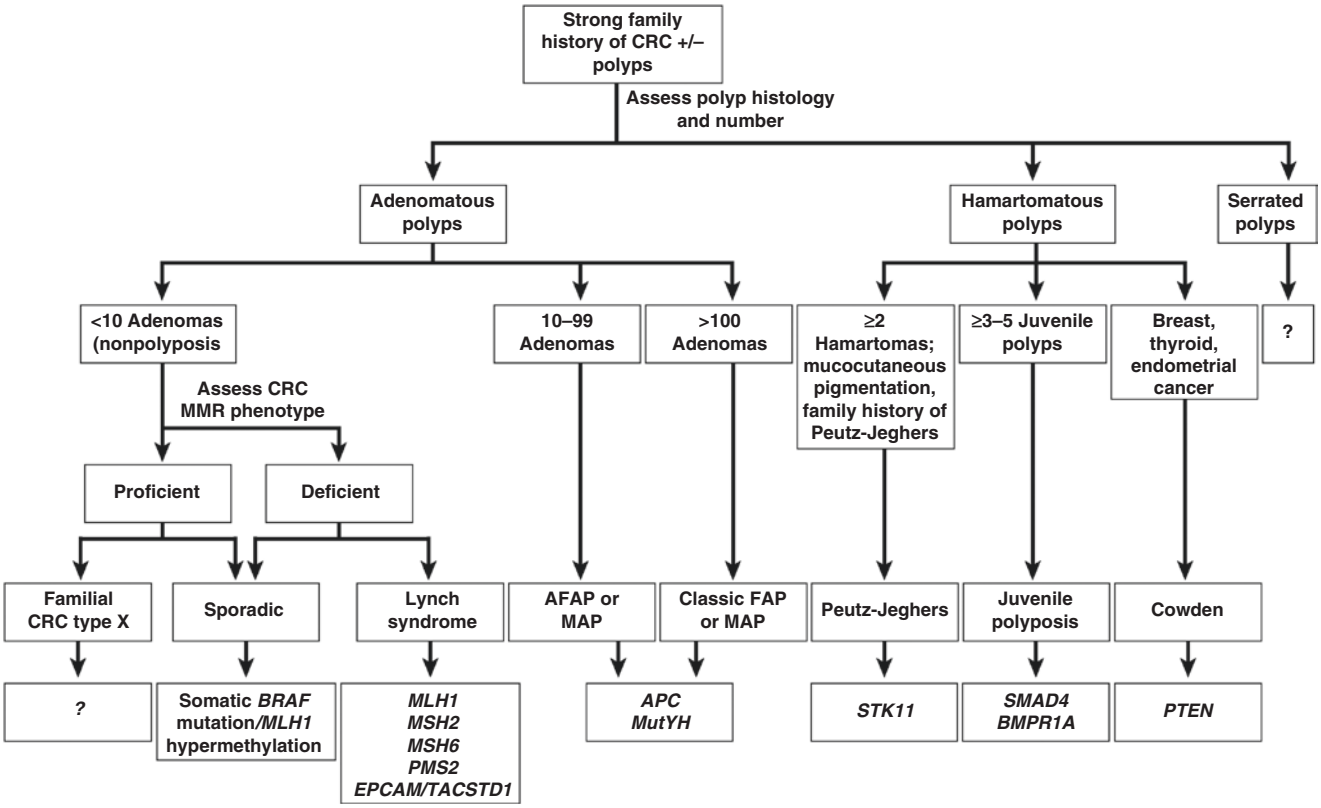


Fig. 33.1 Clinical diagnostic algorithm based on polyp burden. CRC colorectal cancer, MMR mismatch repair, AFAP attenuated familial adenomatous polyposis, MAP MutYH associated polyposis, FAP familial adenomatous polyposis. (Reprinted with permission from Stoffel and Kastrinos [3])

were c.536A>G, p.Y179C and c.1187G>A, p.G396D. The authors went on to propose looking for these common mutations as the first step in their genetic testing strategy. Patients who were heterozygous for one of these mutations subsequently underwent whole-gene sequencing. There were good sensitivity and specificity when using this strategy in a Caucasian Spanish population [7]. Borras et al. proposed extrapolating this testing strategy to other Caucasian populations by including testing for founder mutations adapted for each country in the second step of testing the whole *MUTYH* gene analysis [8].

Hereditary Nonpolyposis Colon Cancer/"Lynch Syndrome"

Problems of Terminology

In the early twentieth century, the University of Michigan pathologist, Aldred Warthin, reported the case of the now well-known "family G" in which a constellation of early-onset colorectal cancer, uterine cancer, and gastric cancer clustered in excess. These findings remained essentially dormant until the 1960s when Henry Lynch, a medical oncology fellow with medical genetics training, began tracking another Midwest family with somewhat similar features. In addition to revisiting the pedigree of family G, he and his colleagues over the next 20 years developed a registry of families with similar features. Originally termed the "cancer family syndrome," the clinical features of early-onset colorectal cancer, early-onset endometrial cancer, autosomal dominant transmission, apparently improved survival compared to sporadic counterparts, and a broader tumor spectrum (including ovarian cancer, uroepithelial cancer, and skin tumors) became apparent. In order to avoid confusion with the so-called cancer family syndrome of Li and Fraumeni (now called Li-Fraumeni syndrome and involving mutations in the *TP53* tumor suppressor gene), the terminology for the cancer family syndrome of Lynch and Warthin was changed to the term "hereditary nonpolyposis colon cancer" or HNPCC, in order to distinguish it from familial adenomatous polyposis. This HNPCC term is somewhat clumsy and overlong, but more unfortunately, perhaps, it would lead one to believe that colorectal cancer is the only important tumor. For these reasons, Boland recommended the term "Lynch syndrome," in recognition of the early work of Henry Lynch. Although the term has entered fairly broad acceptance, there are problems here as well. Lynch syndrome has come to be limited to families in which a pathogenic mismatch repair (MMR) variant has been found. The older term HNPCC continues to be

commonly used to describe families that clinically appear to more or less have the clinical syndrome, but in which no mutation is detected. This in turn can easily be confused with the so-called familial cancer syndrome "X," which by definition is a family that meets Amsterdam criteria for HNPCC but in which there is no evidence of microsatellite instability (MSI) in colorectal or other tumors and in which no MMR mutation is detected. To complicate matters further, the term "Lynch-like" has been coined, typically referring to families with MSI tumors but in which no MMR mutation is detected. The proliferation of terms is problematic at best for cognoscenti and likely baffling to the generalist. The reader is asked to indulge the unfortunate terms, until such time as term(s) better reflecting the underlying molecular basis is offered and comes into common parlance. Meanwhile, for purposes of this discussion, we will use the term HNPCC generically, supplemented as needed with clear modifiers.

Early Working Groups

In the 1970s, investigators in Europe interested in FAP gathered together in England for a workshop in the interest of harmonizing data collection among registries that had emerged for its tracking and management. Some of these, such as those in Denmark, were truly national registries, while others were single- or multi-institutional programs. Members of this so-called Leeds Castle Polyposis Group, or LCPG, continued to meet every 2 years and began to formulate guidelines for FAP management. Because of its narrow focus on FAP, investigators interested in HNPCC formed a parallel society termed the International Collaborative Group (ICG) on HNPCC. This group formed in 1990 and met annually. Shortly after the turn of this century, the LCPG and ICG merged and their working group is now called the International Society for Gastrointestinal Hereditary Tumors (InSiGHT). The group continues to meet biannually. Regional groups for the study of FAP, HNPCC, and other newly emerging GI polyposis and nonpolyposis GI cancers have formed in the Americas (Collaborative Group of the Americas on Inherited Colon Cancer or "CGA-ICC") and in Europe the so-called "Mallorca" group. These working groups can be expected to collaborate in designing future studies.

Molecular Basis for Hereditary Nonpolyposis Colon Cancer: Mismatch Repair Gene Mutations and Microsatellite Instability in Tumors

The major breakthrough in understanding the genetic basis for HNPCC, which has ultimately come to guide many aspects of management, was the discovery of the locus containing the first MMR gene. This was based on a genome-wide search for evidence of linkage between disease expression typical of the HNPCC spectrum and otherwise anonymous genes. This approach was not unlike the basis for establishment of genetic linkage between breast/ovarian cancer and the *BRCA* genes. Only after linkage to a locus on chromosome 2 and recognition of disease-causing mutations in a gene within that region, the *MSH2* gene, was it obvious that the MMR system was the basis for HNPCC. Within a very short time, additional genes within the MMR family were identified: the *MLH1*, *MSH6*, and *PMS2* genes. Over the past 20 years since these genes were identified, a host of important correlations have been drawn.

Pathology

It had been known for some time that DNA mismatches occur in eukaryotes, with research into mechanisms for the identification and repair of such mismatches ongoing in yeast species. Considerable progress has been made in defining a characteristic pathology for HNPCC tumors. Colorectal cancers that occur due to an underlying MMR mutation are commonly poorly differentiated while at the same time remaining diploid. They are characterized by "tumor infiltrating lymphocytes," that is, infiltration of the malignant epithelial cells with mature lymphocytes. In addition, a so-called Crohn's-like reaction occurs, involving peri-tumoral lymphocytic infiltrate. Indeed, astute GI pathologists can have their index of suspicion raised for the possibility of HNPCC simply on the basis of this characteristic pathology. A huge volume of translational laboratory investigation has gradually disclosed the intricate details of the normal and abnormal workings, as well as regulation of the MMR genes [9, 10].

Genotype/Phonotype Correlations

A volume of information from large registries, including population-based registries, has yielded a wealth of information about genotype/phenotype correlations in patients with underlying MMR mutations. In most clinical series, the *MLH1* and *MSH2* genes are the most frequently mutated genes in HNPCC, with each one accounting for about 40% of all mutation-positive cases. *MLH1* is associated with a relatively severe phenotype, with early age of onset being common. *MSH2* is also associated with a severe phenotype. In addition, *MSH2* generally carries the broadest range of extra-colonic tumors. The *MSH6* gene tends to be associated with later age of onset, a higher tendency toward rectal cancer, and a higher risk of endometrial cancer.

PMS2 appears to be the least penetrant MMR gene. It is not uncommon for patients in their 50s, 60s, or older to be found to have a PMS2 mutation, in the relative or complete absence of a family history of malignancy. In fact, rare biallelic mutations in *PMS2* have been reported [11–13]. The phenotype is quite severe, with cancer onset in the teens or younger. When biallelic mutations are present, there is typically no immunohistochemical expression of PMS2, even in normal tissues, hence the term "constitutional" mismatch repair deficiency or "CMMRD." Because of the very young appearance of malignancy, occasionally including brain tumors and hematologic malignancies, such patients are commonly encountered by pediatric oncologists. Biallelic mutations in carriers of *MLH1* and *MSH2* have not been described and are likely lethal in utero.

Population studies have been conducted in which all cases of colorectal cancer are tested for evidence of MSI, either by polymerase chain reaction (PCR)-based assay or by use of immunohistochemistry (IHC). Informative cases are then tested for the presence of an underlying MMR mutation, by means of direct exon sequencing, supplemented by assays for detection of more complex rearrangements, including deletions not detectable with sequencing or alternatively are studied for the presence of somatic methylation of the promoter of the *MLH1* gene. These studies have become more robust as more powerful and nuanced technologies have emerged. The most recent studies indicate that underlying MMR mutations account for only about 1–3% of all colorectal cancers [14, 15].

Microsatellite Instability (MSI) and Distinguishing Sporadic MSI from Hereditary Nonpolyposis Colon Cancer

Microsatellite instability (MSI) is the hallmark of HNPCC tumors. As we now know, microsatellites are short repeat sequences of mono-, di-, tri-, and even tetra-nucleotides (e.g., ACACACACACAC) occurring at both coding and noncoding regions widespread in the entire genome. In malignancies caused by underlying MMR gene mutations, there is typically an increase or decrease in the length of these repeat sequences that can easily be detected by gel electrophoresis, consisting of a different, extra band occurring in the tumor compared with normal tissue. The source of normal reference tissue is typically normal mucosa taken at a surgical margin, although we prefer to take an endoscopic biopsy of normal mucosa at a distance from the tumor edge, submitted separately for the purpose of PCR-based assay. In some cases, such as archived tumor material, micro-dissected normal stroma can be used. Of course, peripheral blood or any other normal tissue can be utilized as a reference. In general, MSI is present when at least several different genes with microsatellite-containing regions are mutated. Panels of MSI markers are used, and in most cases all or nearly all such genes are mutated in HNPCC tumors. If there are no changes in the frameshift length of microsatellites, then the tumor is considered microsatellite stable (MSS). If one mutation is found, the tumor is MSI low, and if two or more microsatellite mutations or frameshift length changes are detected, the tumor is MSI high.

Use of such panels provides an easy way to distinguish HNPCC tumors from sporadic cases. HNPCC tumors virtually always show evidence of MSI, whereas sporadic cases do not. This difference is subject to one very important caveat. MSI can be caused not only by the presence of MMR mutations but also by acquired methylation of the *MLH1* promoter. The frequency of MSI has been consistently determined in large unselected series of CRC at approximately 12–15% of stage II and III colorectal cancers [16, 17]. If in a given population of CRC, 15% have MSI but only 3% have an MMR mutation, then as much as 80% of all MSI cases will be found to be sporadic. Now most of these cases will be older and will have no significant family history of cancer. But if the clinical strategy at a given institution is to query all CRCs for evidence of MSI (see the "Universal Testing" section of this chapter), then some convenient method for distinguishing likely HNPCC from likely sporadic MSI must be found. Fortunately, there are features that reliably distinguish sporadic microsatellite unstable tumors from true HNPCC tumors. This is the presence, noted earlier, of *MLH1* hypermethylation in the sporadic cases. This typically involves methylation of the promoter region of the *MLH1* gene. HNPCC tumors virtually never show hypermethylation. At our institution, our routinely used clinical requisition form provides for the performance of methylation assay in the event MSI is detected. A surrogate for hypermethylation involves the presence of *BRAF* mutations. Virtually, all MSI unstable tumors that are sporadic and that manifest hypermethylation also have evidence of *BRAF* mutations. Conversely, germline mutation-positive HNPCC cases are virtually always wild type (WT) for somatic *BRAF* mutations.

An alternative or surrogate measure of MSI involves immunohistochemistry, discussed later. One problem with the reliance on MSI is the recognition that approximately 15% of all colorectal cancers show evidence of microsatellite instability. As mentioned previously, in most population series, about 80% of these tumors are in older patients with no family history. That these are indeed sporadic is demonstrated by the fact that efforts to detect mismatch repair mutations are negative. Population studies in which MSI (or IHC as a surrogate) are done on all colorectal cancers have MMR mutations detected in only about 20% of this 15% of cases that show microsatellite instability, thus yielding the final figure of 2–3% of all tumors are HNPCC.

Role of Immunohistochemistry

A simpler, cheaper, and in most cases a more informative way to evaluate for MSI is to perform IHC staining for expression of each of the MMR-associated proteins. In practice this works like any other IHC. Tumor slides are stained for proteins corresponding to *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes. Intact staining for all proteins denotes a microsatellite stable tumor. Loss of staining for one of these proteins indicates loss of expression of the corresponding gene and likelihood of underlying germline mutation. This is especially helpful as patterns of IHC expression can help prioritize and limit expensive germline testing.

There are several important cautions to be made when relying on IHC. First, loss of *MLH1* protein may well be an epigenetic change that is somatic in nature. It denotes inactivation of *MLH1* due to the same hypermethylation process that accounts for MSI-H tumors. Second, it is important that there be nontumorous positive control cells, typically stromal elements in the tissue section showing loss of MMR expression. Third, staining may be patchy and at least partially retained in true mutation carriers, especially *MSH6*. Staining may sometimes be retained in *MLH1* mutation carriers, suggesting the presence of protein that is immunoreactive but not functional. Finally, because of the functional heterodimers of *MLH1* with *PMS2* and of *MSH2* with *MSH6*, tumors losing expression of *MLH1* will generally have an obligated, concomitant loss of *PMS2*, and those with MSH2 loss a corresponding MSH6 loss. Notably, population studies such as the Spanish Epicolon study have shown that the correlation between MSI when done by PCR-based assay and MSI as inferred by protein loss by IHC is not perfect. Between 5% and 10% of cases with MSI by PCR will show normal IHC, and a similar proportion with loss of protein expression by IHC will have normal MSI. This is most evident in population-based series such as Epicolon where the overall prior probability for abnormality is low, overall, such that false positives may be more prevalent.

Notwithstanding some of the limitations of IHC, it does appear that reliance on IHC alone has come to dominate the approach to clinically oriented testing. A final, practical note of caution when relying on IHC: If a patient has a high pretest or "prior" probability of having germline MMR mutation (e.g., young, strong family history, no evidence of polyposis) but normal IHC staining, get a second pathology opinion on the staining and/or be prepared to do PCR-based MSI testing. Likewise, when the clinical picture is compelling but initial PCR-MSI is normal, consider IHC. Alternatively, if the tumor assays are normal in the setting of a compelling clinical picture, go ahead with germline mutation testing for all MMR genes (as well as EPCAM, noted later), but with counseling that stresses a low likelihood of mutation detection in the face of normal MSI/IHC.

Several additional points warrant mentioning. When tumor testing is considered, the assumption is that the tumor is, in fact, an invasive adenocarcinoma. It is possible that benign tumors can be informative when malignant tissue is not available. An example might be a patient who is undergoing clinical colonoscopy screening due to a parent with early-onset colorectal cancer. In such cases, there will commonly be no archival tumor tissue from the affected parent available for testing. The parent may be deceased and thus unavailable for direct germline mutation testing. If our patient undergoing colonoscopy is found to have an adenoma but no invasive malignancy, the question becomes the yield of doing PCR-MSI or IHC on that adenoma tissue. Little attention has been devoted to this issue, but at least one report suggests a reasonable yield, at least for large adenomas and those with severe dysplasia [18].

Clinical Decision-Making About Whom to Test

There are three basic strategies for determining which patient merits testing for a germline MMR mutation.

1. Utilize clinical criteria to maximize likelihood that informative patients have tumor tissue selected for MSI/IHC (e.g., "Bethesda Guidelines"—see next section).
2. Test all CRC and perhaps all endometrial cancers for MSI/IHC ("universal" testing).
3. Instead of relying on tumor testing to select patients for further germline mutation testing, simply use risk prediction models to arrive at an acceptable threshold above which to offer mutational testing (e.g., PREMM1, 2, 6 and related models).

Bethesda Guidelines

In the relatively early days of testing for HNPCC, the primary role for evaluating tumors for evidence of MSI was apparent. In the absence of firm data on the yield of testing all tumors for MSI or testing all patients for germline MMR mutations, an expert panel provided recommended threshold clinical criteria that would warrant MSI/IHC. These are the Bethesda Guidelines (Table 33.1) [19].

The panel specified the mononucleotide and dinucleotide markers considered optimal for PCR-based MSI testing (*MLH1*, *MSH2*, *MLH6*, *PMS2*). Not considered directly at the time of this report was the potential for using IHC as a surrogate for PCR-MSI. Subject to the cautionary note above, it is likely that IHC would be recommended as a suitable alternative (Table 33.2) [7].

Several reports have suggested a good yield when applying Bethesda guidelines or some simplified modification of them in clinical practice. However, clinical guidelines can

Table 33.1 Revised Bethesda Guidelines: when to perform MSI testing in colorectal tumors

Colorectal cancer diagnosed in a patient under age 50
If synchronous, metachronous colorectal, or other HNPCC-associated tumors are present regardless of age
Colorectal cancer with MSI-H histology in a patient under age 60
Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-associated tumor with one of the cancers diagnosed before age 50
Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-associated tumors, regardless of age

Adapted from [19]
HNPCC hereditary nonpolyposis colon cancer, *MSI-H* microsatellite instability-high

Table 33.2 Amsterdam II Criteria [4]

At least three relatives with HNPCC-associated cancer (colorectal, endometrial, small bowel, renal pelvis, or ureteral) with all of the following criteria present:
One must be a first-degree relative of the other two
At least two successive generations affected
At least one relative diagnosed with HNPCC-associated cancer diagnosed before age 50
FAP excluded
Tumors verified whenever possible

HNPCC hereditary nonpolyposis colon cancer, *FAP* familial adenomatous polyposis syndrome

often have a high sensitivity for detecting a condition but at the expense of low specificity.

Universal Testing

However positive the yield may be when applying clinical criteria for selecting patients for tumor and/or germline testing, one question that persists is "Are there patients with germline MMR mutations for HNPCC that would be missed with application of clinical selection criteria? If so, how many are there and can they be predicted in any other way?"

Such questions logically led to the performance of several very important population studies. These essentially demonstrate that there are a small proportion of cases with MMR mutations that would not have been identified by Bethesda or even "relaxed" Bethesda-like guidelines. More recent series have suggested that a higher proportion of such cases are found to have *MSH6* and *PMS2* mutations. This should not be surprising, given the lower penetrance of these genes.

Predictive Models

A major disadvantage of clinical decision-making based on tumor testing is the need for such a tumor and the costs associated with the PCR-MSI or IHC. If suitable selection criteria existed on which to predict mutation likelihood in the absence of tumor testing, these issues disappear. One decision model, PREMM1, 2, 6, was subjected to a further modeling exercise in which it was concluded that germline mutation testing in patients with a >/+ 5% prior probability of mutation would be cost-effective [20]. The PREMM1, 2, 6 model does not use any data from tumor testing (Fig. 33.2) [21] but rather is based on personal or family history of tumors in the spectrum of HNPCC, taking age of onset and number or affected relatives into account.

Use of predictive models can be helpful in clinic when counseling otherwise healthy patients having a family history of colorectal and other cancers. The quick bedside calculation of risk can often be reassuringly low and can help dissuade from mutational testing that has a very low yield.

Testing Algorithms and Operational Issues for Genetic Counselors

Whether selective or universal tumor testing, or risk assessment model-based testing is employed, there are reasonably straightforward algorithmic approaches to the workup of colorectal cancer patients for possible HNPCC. The details of the workup are important, but so is the clinical practice model in which the work is done.

The first step is to determine whether to test a given malignancy for MSI at all. Most clinical practice guidelines do favor use of tumor-based testing with either PCR-MSI or IHC. This is increasingly either universal (testing all CRCs) or a simple modification of universal testing (all cases below age, 70, 60, or 50, depending on local resources). In others, more narrow clinical selection criteria may be employed (modifications of Bethesda guidelines). In all such circumstances, it is essential that the clinical unit have procedures in place for routine performance of the testing. This requires clarity regarding the criteria for testing (if not strictly universal), assignment of responsibility for the ordering of testing, and an understanding of the role for genetic counselors (or otherwise suitably trained personnel). This latter point is important. Not all patients whose tumor is tested will necessarily need to see a genetic counselor. The counselor is usually in the best position to review all of the issues that are relevant: age of patient, presence or absence of family history, presence or absence of multiple polyps, and results of MSI/IHC. In the interest of efficiency, this can and should generally be accomplished through a simple review of the medical record. Thus, an older patient with unremarkable family history and either an MSS tumor or MSI-H tumor with hypermethylation or *BRAF* mutation requires no further consideration for underlying genetic susceptibility.

The less selective the clinical criteria, the greater the likelihood that a given case of MSI will be sporadic, as 80% of

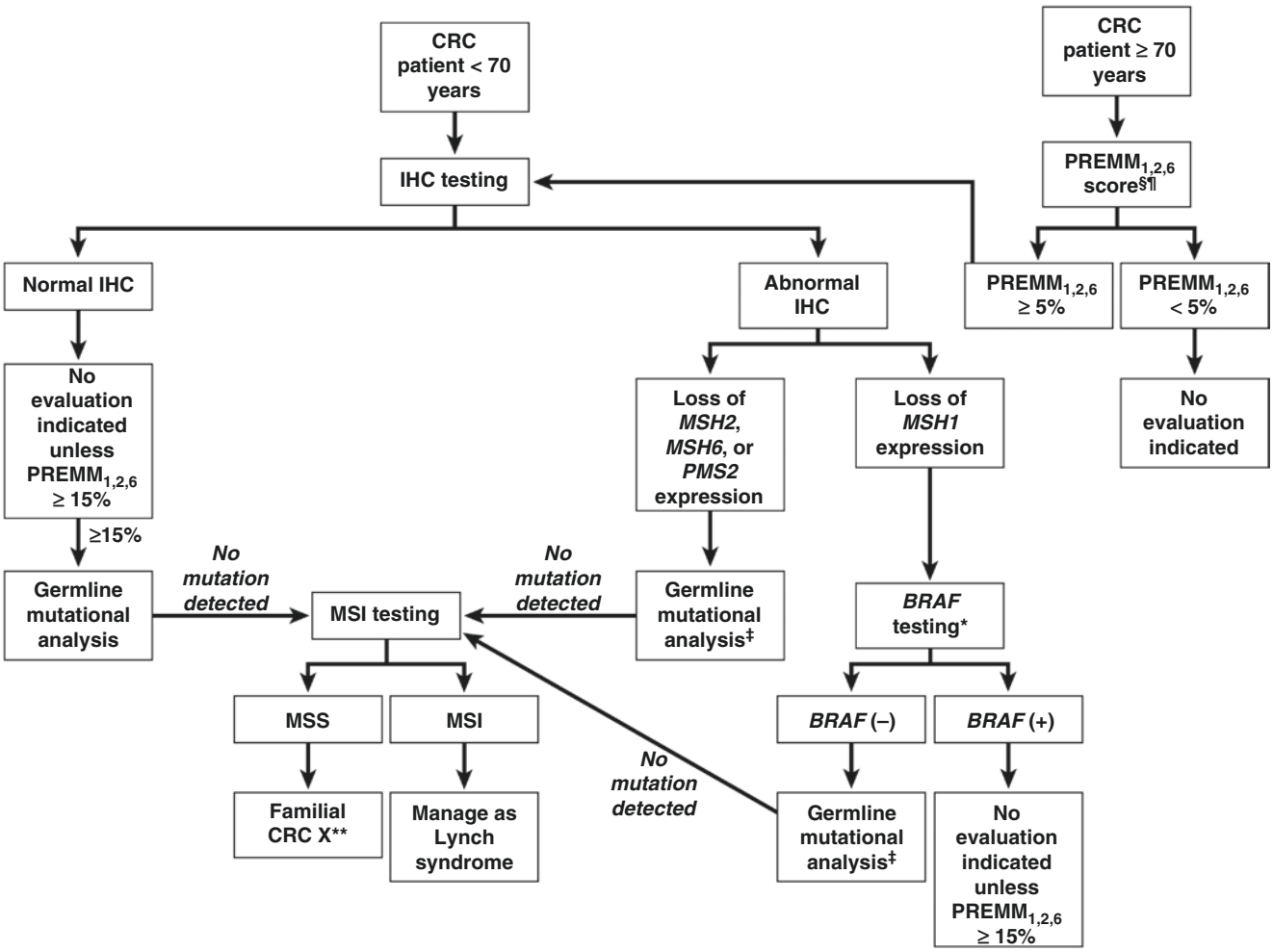


Fig. 33.2 Clinical diagnostic algorithm for tumor testing. CRC colorectal cancer, IHC immunohistochemistry, MSS microsatellite stable. § $PREMM_{1,2,6}$ (Prediction of Mismatch Repair Gene Mutations in *MLH1*, *MSH2*, and *MSH6*) score can be calculated at http://premm.dfci.harvard.edu/. Other models (MMRpro, MMRpredict) may also be used with their own specified cut-off scores. ∗*BRAF* testing: (+), mutation present; (−), mutation absent/wild type. ∗∗Surveillance recommendations based on personal and family history. ‡Gene-specific germline mutational analysis. (Reprinted with permission from Kastrinos and Stoffel [21])

all MSI-H cases are sporadic. A simple means of further distinguishing these is thus important. Most institutions that routinely perform MSI/IHC with a low threshold (universal or near-universal testing) do also routinely perform a methylation assay or *BRAF* mutation assay. Only cases with no methylation and wild-type *BRAF* are then referred on for genetic counseling in anticipation of mutational testing.

Hereditary Nonpolyposis Colon Cancer and Microsatellite Instability in General Carry a Prognosis and Sensitivity to Chemotherapy That Differs from Microsatellite Stable Tumors

One of the earlier observations in HNPCC was a tendency toward improved survival [10, 22]. This was the case even before any of the MMR genes were discovered. The earliest observation was really before any organized screening efforts had begun that would have improved survival through early diagnosis [23]. Moreover, early diagnosis through screening would have led to an earlier average stage at diagnosis, but even the original reports on survival adjusted for stage at diagnosis.

Post-hoc analyses of large cooperative trials have now consistently shown that patients with microsatellite instability-high (MSI-H) tumors experience better stage for stage survival compared with microsatellite stable tumors [17, 24, 25]. Some of these same trials have demonstrated that within-stage differences in response to 5-fluorouracil (5-FU)-based therapies exist between MSI and MSS tumors [24].

What the post-hoc analyses from these trials have not been able to distinguish is whether there are differences in prognosis or treatment response within the MSI group. Put

another way, we do not know whether there are differences between mutation-positive HNPCC patients and their sporadic counterparts, since the trial databases have not reliably distinguished these populations. Patients with colorectal cancer deficient in MMR genes had lower rates of tumor recurrence, longer time to tumor recurrence, and improved survival rates compared to those with proficient MMR genes when treated with 5-fluorouracil [24].

The MOSAIC adjuvant therapy trial (oxaliplatin/fluorouracil/leucovorin) of stage II and III CRC demonstrated that addition of oxaliplatin improved 3-year disease-free survival (DFS) and 6-year overall survival (OS) [26]. An update focusing on 10-year OS/DFS by mismatch repair status and *BRAF* mutation showed that while *BRAF* mutation status was not independently predictive of survival benefit, patients with MSI tumors treated with oxaliplatin experienced a favorable OS at a level of $p = 0.014$ compared with those receiving 5-FU/leucovorin alone [27]. As with other similar trial analyses, the low prevalence of patients with MSI tumors (only 9.4% in this series) limited the power to detect treatment differences.

Genetic Counseling and Testing in At-Risk Relatives

To the clinicians treating existing tumors, the emphasis rightly is placed on the management of that tumor, and our commentaries on scope of surgery decision-making, survival features, and chemotherapy responsiveness have addressed this. We have also addressed survivorship issues having to do with clinical surveillance for new colorectal, other GI, and extraintestinal tumors. However, it is incumbent upon us to reckon with the fact that, for family management purposes, our index CRC case found to have an MMR mutation is simply that: the first case found in that family. Depending on the size and composition of the family, there may be tens to hundreds of individuals potentially at risk of carrying the same pathogenic variant as that harbored by our index case. These identifiable individual relatives will benefit from knowledge of their risk, from predictive genetic testing, and from clinical surveillance essentially identical to that offered as a survivorship program for the index case.

Clinical practice guidelines make it very clear that relatives should be offered genetic counseling and testing. The clinician most familiar with risk assessment, counseling, predictive laboratory testing, and surveillance can and should be involved in these processes. But these processes are very time-consuming and each discussion also can be very time-consuming. As such, the genetic counselor provides invaluable assistance in educating at-risk patients about their risk and the pros and cons of genetic testing. When performed properly, the elements of informed consent to undergo genetic testing call for a necessarily involved discussion [28]. In the USA, there are a host of commercial laboratories to choose from and issues of insurance coverage commonly need to be worked through. For better or worse, genetic counselors become very conversant with these issues.

The notion of starting with a disease-affected patient, testing for and finding a disease-associated mutation, and then moving on to predictive testing of at-risk relatives is termed "cascade" testing. The points referred to earlier that deal with the genetic counseling/testing process for the at-risk relative should make perfect sense, even if somewhat involved and beyond the scope of practice for the individual practitioner. Yet, this process is child's play compared to the challenges of identifying just who in the family is at risk and communicating the existence of that risk to them.

The standard of care in the USA and other Western countries for risk notification basically consists of the counselor providing the index case with a sense of the need for them to communicate to at-risk relatives the importance of their undergoing counseling/testing. This is commonly reinforced by giving the index case printed materials about the condition in question, that they may pass this along to at-risk relatives. The reality is that this standard, even when met, is generally very ineffective in reaching very many relatives.

A host of barriers exist. Despite the counseling, the index patient may not feel an understanding of the technical information, fearing much will be lost in the translation. Many families suffer from dysfunctional communication patterns, with either the index patient or the at-risk patient being cut off. Even in families that are well educated and communicative, more distant relatives (cousins, etc.) may simply not have been contacted for decades or may not even be known at all.

If it is recognized that the index patient may not be in an ideal position to communicate such critical information to relatives, might there be a role for the provider in doing so? Just as barriers exist for the patient, barriers exist for the provider. The most obvious barrier is the simple fact that our clinical practice models do not really provide for care beyond the index patient, unless one or more relatives simply happen to become our patients themselves. We simply do not have the time or the support structure for doing so as a part of routine clinical service. Some institutions have registries that have the potential for following extended families. But until conditions such as HNPCC become more "mainstream" the resources for such efforts are harder to identify and to rationalize. Any such effort would be conducted under the notion of research, but the issues to be addressed are frankly those of clinical management. Whether considered a research or clinical undertaking, prevalent and otherwise appropriate concerns over confidentiality and privacy carry a chilling effect on even the most well intentioned of undertakings. Another chilling effect is the doctrine of

"genetic exceptionalism." This is the notion, discredited by most in the field but nevertheless prevalent in some circles, that presupposes that genetic information is somehow taboo and not something that can be managed in a routine clinical fashion, not unlike the way in which psychiatric records are sometimes regarded.

In many respects, the gap between the needs of at-risk relatives and our ability to address them suggests the need for reframing the entire conversation in terms of a public-health model. Fortunately, there are models that can be looked to. Suthers, writing on behalf of the clinical genetics service unit for the State of South Australia (Adelaide), in 2008 described an approach in which counselors offered to directly contact at-risk relatives of patients with MMR and *BRCA* mutations [29]. Index cases simply completed a form listing names and postcodes of at-risk relatives. The clinical services unit then corresponded with relatives, providing form letters summarizing the nature of risk and offering counseling within South Australia or referral to providers in other Australian states. The program was able to approximately double the number of at-risk relatives identified and tested. Very few complaints were lodged over "inflicted insight" or other such issues. Index cases were encouraged to talk to their relatives in whatever fashion was felt best, but such communication was to be considered as "in addition to" rather than "instead of" communication from the genetics services unit. Very few cases existed in which the index case explicitly asked that a relative not be contacted. The basic features of this program continue to the present time (Nicola Pawlowski, personal communication). A very similar program is now operating at a national level in New Zealand (Susan Parry, personal communication). It is true that these units operate as a component of the respective health ministries in these countries, are budgeted as such, and carry the respect and authority that the health ministries otherwise possess. As such, the exact model might not translate precisely to the USA or to other jurisdictions. What the programs in South Australia and New Zealand offer are models for consideration. They show the "art of the possible" and as such pose a challenge to those of us in other countries in which the lack of suitable health-delivery models or lack of will continue to compromise getting service to those in need in a way that works.

Clinical Surveillance and Clinical Practice Guidelines

Let us take the case of two MMR mutation carriers: the index patient who has undergone curative resection with or without further chemotherapy, tested on the basis of MSI status or other clinical features warranting mutational testing, and the case of the at-risk relative found to have the same mutation in the setting of predictive testing triggered by the diagnosis of the index case. Depending on age, both would be considered for essentially the same clinical surveillance. Existing clinical practice guidelines exist from several independent sources, including the National Comprehensive Cancer Network (NCCN) as well as the combined GI societies of the American Gastroenterology Association (AGA), American Society of Gastrointestinal Endoscopy (ASGE), European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the American Society for Colorectal Surgery (ASCRS). Although some minor differences do exist, these are remarkably consistent with one another. They provide algorithms for the evaluation of cancer patients for MSI (some recommending universal testing, citing the EGAPP, while others making more generous provision for clinical decision-making). They all endorse predictive testing.

The various clinical practice guidelines provide recommendations for clinical surveillance in survivors and in asymptomatic mutation carriers (sometimes termed "previvors" by advocates). Essentially, all provide levels of evidence for the recommended surveillance strategies. The only surveillance strategy for which support exists on the basis of well-conducted observational trials (no randomized controlled trials exist for surveillance strategy or interval) is that of optical colonoscopy [30]. The usually recommended interval for *MLH1* and *MSH2* mutation carriers is 1–2 years, beginning at age 20–25. Note that both the recommended ages at initiation and interval provide for a degree of discretion on the part of the provider based on various clinical considerations. In light of the lower penetrance for *MSH6* and especially for *PMS2*, there is a growing tendency toward liberalization of the age at initiation (30–35), but not for longer intervals, as there are insufficient data on differences, by gene, in the pace of the adenoma to carcinoma sequence. The small observational trials that support these approaches are themselves supported by partly retrospective, partly prospective cohort observations from the international Cooperative Family Registry (CFR) and a European cooperative data collection depicting short cancer risks in groups under surveillance more or less according to the above guidelines [31, 32]. The European study, in particular, expresses concern about relatively high rates of interval cancers despite surveillance at these intervals. Yet the numbers of cases are small enough as to likely defy analysis over the issue of colonoscopy quality (prep quality, operator's adenoma detection rate or ADR, etc.) versus tumor biology (aggressive growth). Such findings certainly invite innovation at the level of surveillance tools (CT colonography, mutation DNA in the stool) and intervals—ideally in randomized trials.

If controversy exists with respect to the best approach to colon neoplasia surveillance, there is much less basis for any recommendations for surveillance beyond the colon. Extra-colonic screening recommendations are predicated on lifetime risks of cancer and clinical prudence, not rigorous observational trials, much less randomized trials.

Upper Gastrointestinal Tract Surveillance

In the absence of any meaningful observational data, the NCCN recommends testing and treating for *Helicobacter pylori* infection of the stomach, and for periodic upper GI (UGI) endoscopy for those from high-risk geographies and for those with immediate family history of UGI cancer. There is some suggestion that stomach and small bowel cancer risk is appreciable mainly for *MSH2* carriers, somewhat or much less so for *MLH1*, *MSH6*, and *PMS2*. Our practice is to offer UGI endoscopy to MSH2 carriers with an effort to reach at least the proximal jejunum, performed at the time of alternate colonoscopy, thus at intervals of about 2–4 years. In non-*MSH2* carriers especially, any surveillance of the UGI tract has to be predicated upon individual considerations.

Because the risk of small bowel tumors is increased, the question is raised regarding possible approaches to the jejunum and ileum, beyond the reach of conventional UGI endoscopy. If such assessment were to be done, capsule enteroscopy would be the tool of choice. Indeed, one trial does exist, albeit essentially negative [33].

The risk of pancreatic cancer is at least marginally increased in HNPCC. However, major limitations exist for screening even in those at highest risk, such as use of magnetic resonance pancreatography (MRP) and endoscopic ultrasound in those with Peutz-Jegher syndrome and *CDKN2A* mutation carriers [34]. Consequently, there can be no recommendation at present for pancreas screening in general for MMR mutation carriers. Exceptions may exist for those with an immediate family history of pancreatic cancer, but even here any decision in favor would have to be entirely empiric, likely in response to major patient anxiety.

Gynecologic Surveillance

The risk of endometrial cancer is second only to that of colorectal cancer in HNPCC. In fact, many HNPCC patients will present with endometrial cancer as their sentinel event. As such, the uterus should be an important target of clinical attention, both for surveillance in at-risk patients and for universal tumor testing in patients with endometrial cancer. Risk of ovarian cancer is also increased in HNPCC, and in general is a much more feared malignancy than is endometrial. The cumulative risk of uterine cancer varies with the specific MMR mutation present and ranges from 15 up to 70% (in patients with *MSH6* who have the lowest risk). The cumulative risk of ovarian cancer can be as high as 22% (patients with *MSH2* and *MSH6* at higher risk) [35]. The most commonly employed tool for screening for both diseases is annual transvaginal ultrasound (TVUS). However, interpretation can be challenging in premenopausal women resulting in poor sensitivity and specificity with this modality.

Surveillance is recommended for endometrial cancer in patients meeting Bethesda criteria or those patients with identified MMR mutations with an annual combined imaging and biopsy approach. The best data on ovarian cancer screening come from trials in BRCA mutation carriers, where the risk of ovarian cancer far exceeds that in HNPCC. Several observational studies have evaluated the impact of screening for ovarian and endometrial cancer in patients with HNPCC and data have been disappointing. Let us take one example: 175 women with HNPCC were enrolled in a screening program. Eleven cases of endometrial cancer were diagnosed through screening with only nine diagnosed/suspected on biopsy and four with suspicious findings on TVUS. Four women were diagnosed with ovarian cancer, none of them through the screening tests [36]. Being enrolled in a screening program should translate to a survival benefit for patients. However, this has not been demonstrated with endometrial cancer and there is a scarcity of studies even evaluating the effectiveness of ovarian cancer screening.

Tissue sampling is, of course, the gold standard. Toward that end we have piloted a so-called "combined screening" program. Women with MMR mutations who are otherwise undergoing periodic colonoscopy were invited to undergo endometrial biopsy while under sedation for the colonoscopy procedure, eliminating the need for a separate visit and procedure, and offering sedation that would otherwise be difficult to rationalize. Our data showed that this was very well received by the women engaged in the program. Biopsy yield data are not yet mature, but early findings suggest a good yield for hyperplasia and atypical hyperplasia. No cancers have yet been detected, but no interval cancers have been observed either [37].

In light of the limitations of both endometrial and ovarian cancer surveillance, an obvious question is the role of prophylactic total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO). Since the risk of primary peritoneal carcinoma is not the concern in HNPCC that it is in HBOC, outcome data on our institutional series of women undergoing TAH/BSO showed no risk of postoperative endometrial or ovarian cancer. Current recommendations are for women who are carriers of MMR mutations to undergo TAH/BSO once they have completed childbearing.

Polyposis Syndromes Other than Familial Adenomatous Polyposis

Peutz-Jegher Syndrome

Peutz-Jegher syndrome (PJS) is inherited as an autosomal dominant disorder. It is much rarer than FAP and should never be confused with FAP. It is caused by the *STK11* gene and the great majority of patients will be found to have a

pathogenic variant in this gene. The most characteristic distinguishing clinical feature is the presence of small pigmented freckling of the lips and buccal mucosa or fingers. Since these are fairly subtle in most cases and cause no symptoms, they can commonly be overlooked. These patients are at risk for cancers of the breast, pancreas, colon, small intestine, and stomach.

The most common presenting symptoms generally do involve the GI tract. A typical presentation will be abdominal pain due to obstruction in the teenage years or younger, commonly due to intussusception of the small bowel related to the presence of a large polyp. These polyps, hamartomas, are the other characteristic defining feature of PJS along with the noted freckling. These hamartomas may at times be difficult to distinguish from juvenile polyps (see "Juvenile Polyposis" in next section), but the pathology characteristically involves smooth muscle strands extending in finger-like projections interdigitated between exuberant glands. The glandular epithelium itself may show areas of cystic dilation akin to those seen in juvenile polyps and, like juvenile polyps, are nondysplastic. However, foci of dysplasia may emerge and form the basis for risk of adenocarcinoma in any part of the colon, small bowel, or stomach. The polyps can involve any part of the GI tract. Considerable variability can exist between members of the same family with respect to the severity of polyp involvement and the area of the gut involved.

Peutz-Jegher hamartomas typically have a very long stalk. This makes even very large polyps fairly easy to remove endoscopically. We generally do not undertake to aggressively remove small polyps unless they are few in number, preferring to focus on larger polyps that have formed a stalk. This is a reasonable approach both in the colon and small bowel.

Of particular importance to the oncologist is the risk of extraintestinal malignancy, most notably involving the breast, pancreas, and reproductive organs. While most PJS patients will be followed by endoscopists concerned with the GI polyps, as described earlier, the care of such patients really requires a multidisciplinary approach and it may fall to the oncologist to coordinate such care.

Surveillance guidelines in PJS do exist and are rather draconian (Table 33.3) [35, 38]. Surveillance is ideally overseen by clinicians in a high genetic-risk breast and gynecology clinic, and typically involves aggressive breast and pelvic imaging. No recommendations exist for mastectomy. However, consideration may be given to oophorectomy based on considerations similar to those for women with *BRCA* mutations—namely, increased risk of cancer with high mortality and suboptimal measures for early detection.

Surveillance for pancreatic cancer poses special challenges. Patients with PJS carry a lifetime risk of pancreatic cancer that may be as high as 20% [39]. The notion of prophylactic pancreatectomy raises the extraordinary issue of surgical risk and postoperative diabetes and exocrine pancreatic insufficiency. Historically, measures for early pancreatic cancer detection have been entirely unsatisfactory. Recent improvements in imaging, involving magnetic resonance targeting the pancreas, complemented by endoscopic ultrasound have shown some promise [34].

Table 33.3 Surveillance guidelines for patients with Peutz-Jegher syndrome

Organ	Patient age (years)	Surveillance interval	Surveillance exam
Colon	8 (if no polyps resume at 18)	3 years	Colonoscopy
Stomach	8 (if no polyps resume at 18)	3 years	EGD
Small bowel	8 (if no polyps resume at 18)	3 years	Capsule endoscopy
Pancreas	30	1–2 years	MRCP or EUS
Breast	25	1 year	Breast MRI and MMG
Endometrial/ ovarian	25	1 year	Pelvic exam and ultrasound (trans-pelvic or transvaginal)
Cervix	25	1 year	Pap smear
Testicular	Birth to teenage years	1 year	Testicular exam, ultrasound if abnormal exam
Lung	n/a	n/a	Smoking cessation

Adapted from [35, 38]
EGD esophagogastroduodenoscopy, *MRCP* magnetic resonance cholangiopancreatography, *EUS* endoscopic ultrasound, *MRI* magnetic resonance imaging, *MMG* mammography

In summary, the key principles of management of PJS include regular endoscopic surveillance augmented by a multidisciplinary approach to surveillance of extraintestinal organs at risk, in the interest of early cancer detection and prevention. We are not aware of any data suggesting that the natural history or management of locoregional or advanced malignancy in PJS tumors differs appreciably from sporadic counterparts.

Juvenile Polyposis

Juvenile polyps may occur sporadically in infants, children, and adults. Considerable histologic overlap exists between juvenile and inflammatory polyps, with the main feature being prominent cystic dilation of nondysplastic but exuberant glands. When sufficiently numerous, extending beyond early childhood, or particularly when associated with any family history of similar involvement, the presence of juvenile polyposis syndrome (JPS) should be suspected. JPS is most commonly caused by pathologic mutations in the *SMAD4* gene. Less commonly, mutations in the *BMPR1A* gene cause a nearly identical clinical picture. It is likely that

other genes yet to be identified can also cause JPS. As with Peutz-Jegher syndrome, marked variation in severity (age at onset, polyp count) may exist within the same family. As with PJS, the polyps themselves are nondysplastic, but foci of dysplasia with attendant cancer risk can occur. The tendency toward dysplasia and cancer in polyps seems more typical in some families than others.

Although polyps may involve the small bowel, risk of intussusception appears much lower than in PJS. Several significant clinical features have emerged in recent years as particular sources of concern to those managing patients with JPS. In some patients, the number, size, and confluence of juvenile polyps of the stomach are associated with refractory anemia. In such cases, prophylactic gastrectomy may be required. While it is not clear that gastric cancer risk is limited to such cases of severe gastric polyposis, the difficulty in aggressively sampling polyps already causing problems of anemia makes it easier to arrive at a decision in favor of prophylactic gastrectomy.

Another clinical complication in some families with JPS is the concomitant presence of hereditary hemorrhagic telangiectasia. The Cleveland Clinic group has written an excellent review of the association and the surveillance and management measures to be undertaken [35, 40].

Hereditary Gastric Cancer

Gastric cancer is more common worldwide than in North America and is associated with several environmental risk factors, the most recognized being *Helicobacter pylori* infection. Familial clustering of gastric cancer is seen in 10% of cases in the general population where gastric cancer in a first-degree relative confers a two- to threefold risk to an individual [41]. Up to 3% of familial gastric cancer occurs in the setting of hereditary diffuse gastric cancer (HDGC) [42]. HDGC is associated with a mutation in the *CDH1* gene that codes for E-cadherin, a protein responsible for cell-to-cell adhesion and epithelial integrity. The mutation detection rate can be up to 50% when multiple family members have diffuse gastric cancer under the age of 50 [43]. Mutation in the *CDH1* gene confers a cumulative risk of gastric cancer of 80% by age 80 with a mean age of diagnosis at age 40 [44]. Women with a *CDH1* mutation are uniquely at risk for lobular breast cancer with a 60% lifetime risk [44]. Clinical criteria for testing individuals for *CDH1* germline mutations are described [44].

The only way to eliminate risk of gastric cancer among patients with a *CDH1* mutation is prophylactic total gastrectomy. The timing of referral to a surgeon is individualized to each particular patient. Grossly normal gastrectomy specimens will often show microscopic foci of signet ring cells on histopathology. Patients may opt for annual surveillance endoscopy while they are considering gastrectomy. Upper endoscopy should be performed by an experienced gastroenterologist with sufficient time taken to examine all segments of the gastric body and antrum. In our experience, greater than 50 biopsy specimens should be obtained from different segments of the stomach with special attention paid to any mucosal abnormalities. Even perfectly normal exams can reveal signet ring adenocarcinoma on histopathology prompting referral for surgery (Figs. 33.3, 33.4, 33.5, 33.6, 33.7, and 33.8).

Apart from HDFC, there is also an increased risk for gastric cancer—both diffuse and intestinal types—in many other hereditary cancer syndromes including HNPCC, FAP, PJS, Li-Fraumeni, and Cowden syndrome (Table 33.4). Patients affected by these syndromes who are living in areas of high incidence of gastric cancer carry a greater risk, suggesting the possible influence of environmental factors [42].

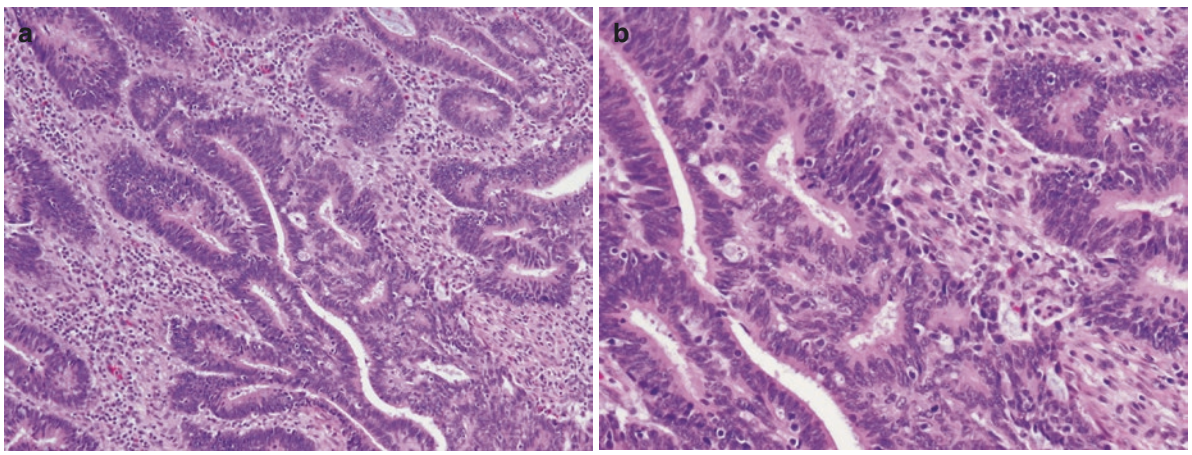


Fig. 33.3 (**a–j**) Intra-tumoral lymphocytes and mucinous differentiation. (Figures courtesy of Deyali Chatterjee MD, Department of Pathology, University of Texas MD Anderson Cancer Center)

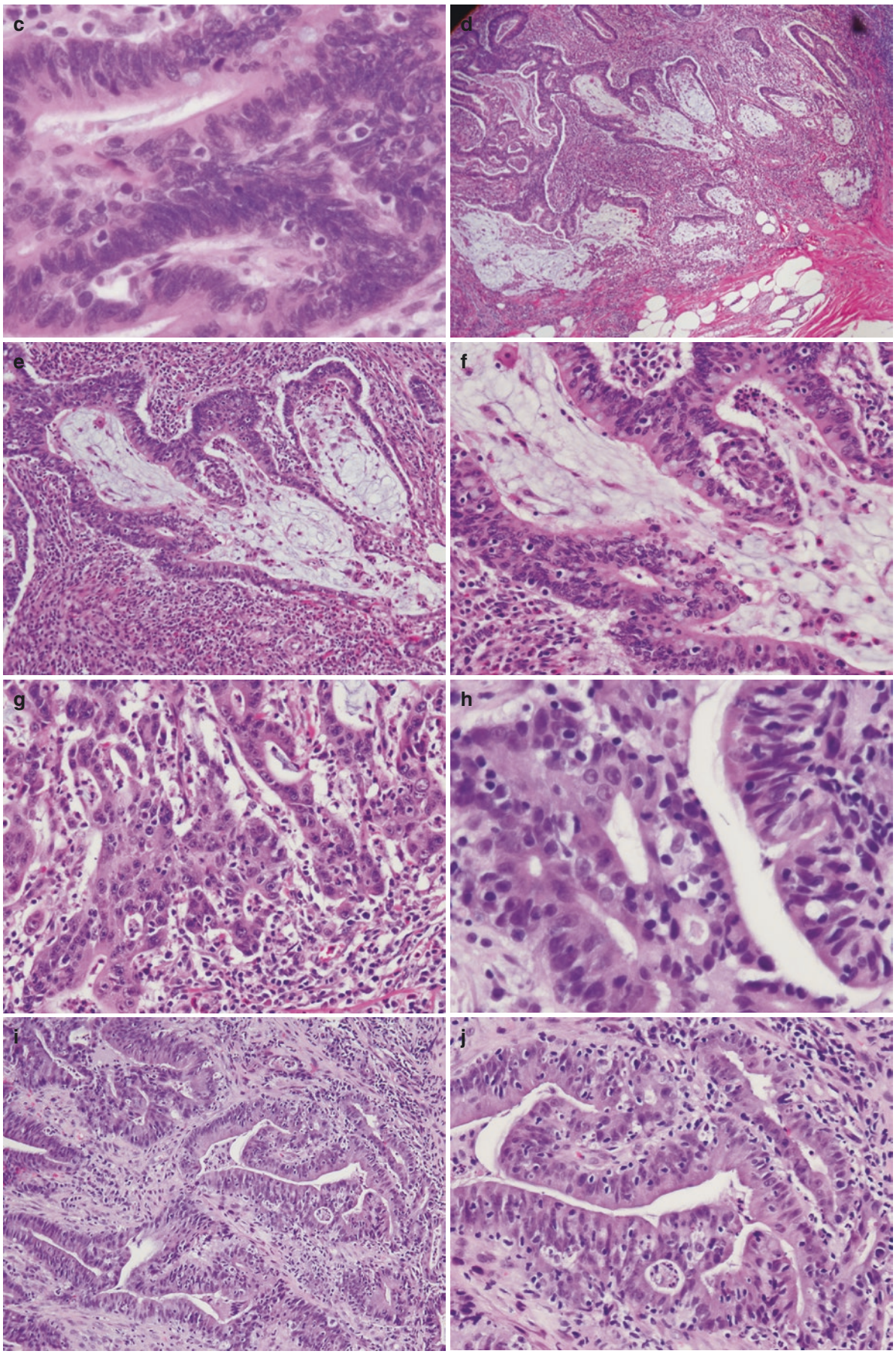


Fig. 33.3 (continued)

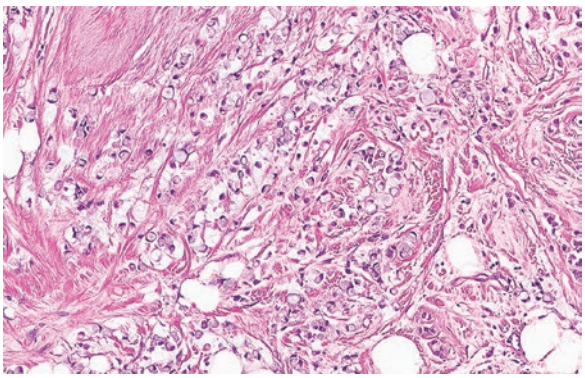


Fig. 33.4 Invasive lobular carcinoma with signet ring features 20×. (Courtesy of Tim Foo MD, Department of Pathology, University of Texas, MD Anderson Cancer Center)

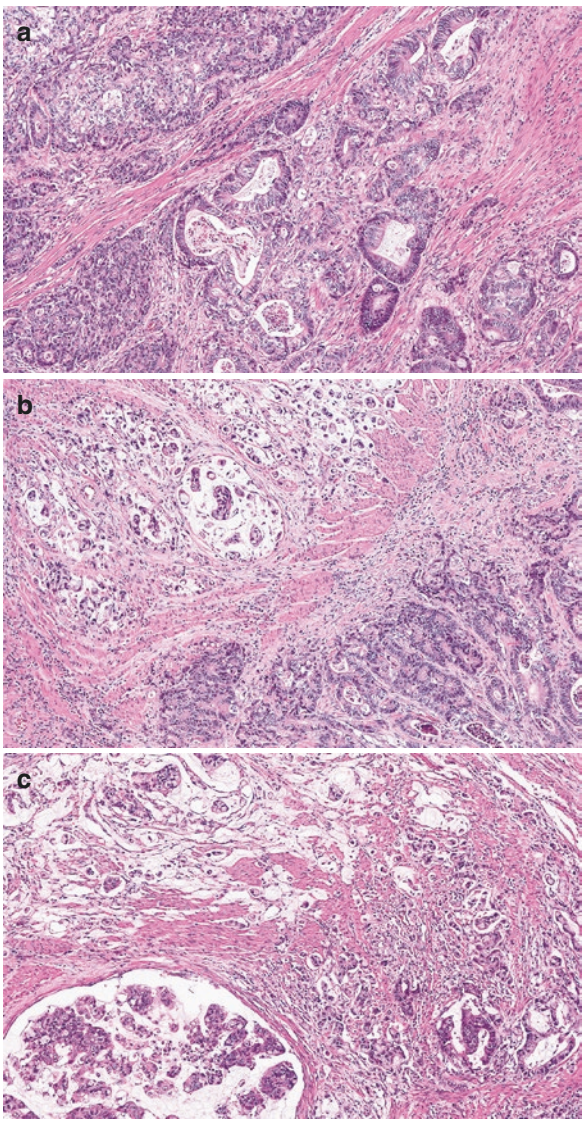


Fig. 33.5 (**a**–**c**) Adenocarcinoma variegated 10×. (Figures courtesy of Tim Foo MD, Department of Pathology, University of Texas, MD Anderson Cancer Center)

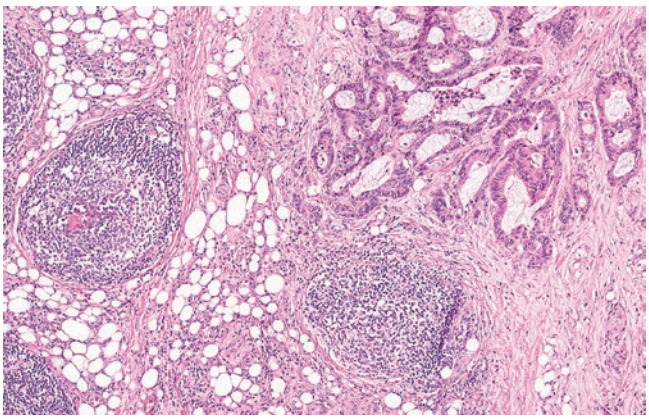


Fig. 33.6 Adenocarcinoma with Crohn's-like response 10×. (Courtesy of Tim Foo MD, Department of Pathology, University of Texas, MD Anderson Cancer Center)

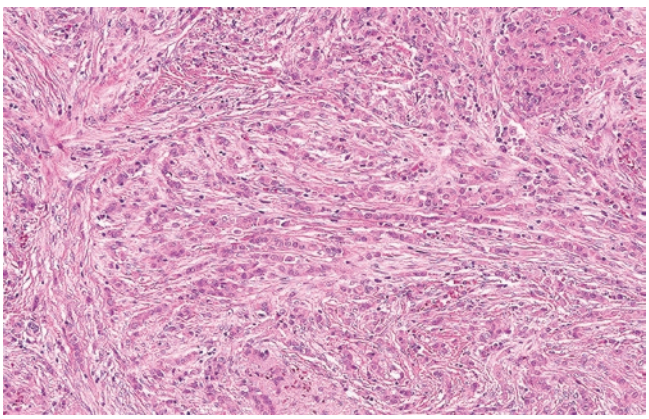


Fig. 33.7 Invasive lobular carcinoma 20×. (Courtesy of Tim Foo MD, Department of Pathology, University of Texas, MD Anderson Cancer Center)

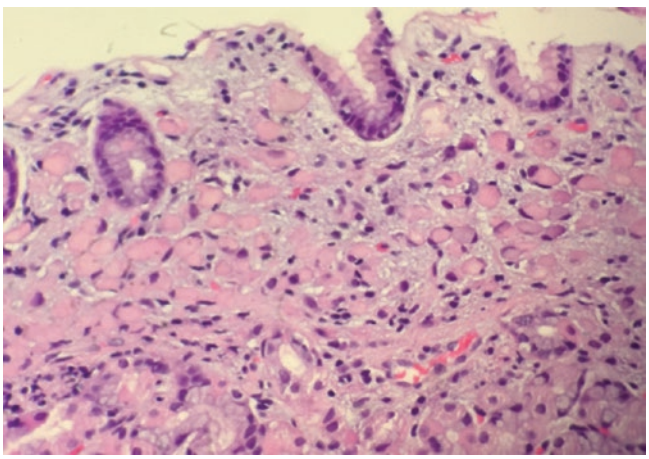


Fig. 33.8 Signet ring adenocarcinoma seen on routine gastric biopsy. (Courtesy of Deyali Chatterjee MD, Department of Pathology, University of Texas MD Anderson Cancer Center)

Table 33.4 Genetic syndromes with risk of gastric cancer

Syndrome (decreasing risk of gastric cancer)	Gene mutation
Hereditary diffuse gastric cancer	CDH1/CTNNA1
Li-Fraumeni syndrome	TP53
Peutz-Jegher syndrome	STK11
Familial adenomatous polyposis	APC
Hereditary breast/ovarian cancer syndrome	BRCA1/BRCA2
Hereditary nonpolyposis colon cancer	MLH1, MSH2, MSH6, PMS2
Juvenile polyposis syndrome	SMAD4/BMPR1A

Hereditary Pancreatic Cancer

As in gastric cancer, the majority of pancreatic cancer cases is sporadic, with 5–10% related to either familial clustering, inherited risk for pancreatitis predisposing one to cancer, or in the setting of a hereditary cancer syndrome. Individuals with two to three relatives with pancreatic cancer (one of whom is a first-degree relative) or two first-degree relatives with pancreatic cancer should undergo screening themselves [34]. There is no consensus on the appropriate age to start screening. However, it is suggested to begin at age 40 or at 10 years younger than the youngest affected relative. Pancreatic adenocarcinoma is associated with many hereditary cancer syndromes with PJS conferring the greatest lifetime risk (36%), familial atypical multiple mole melanoma syndrome (16%), and HNPCC (9%) [45–47]. Familial breast and ovarian cancer are associated with germline mutations of *BRCA1* and *BRCA2* and are at risk for pancreatico-biliary and gastric cancer. Specifically, *BRCA2* carriers carry a higher risk for pancreatic cancer (up to tenfold) compared to *BRCA1* carriers (up to fourfold) [48]. Patients with hereditary pancreatitis have a *PRSS1* mutation that predisposes them to early-onset and chronic pancreatitis as well as a significant lifetime risk of up to 50% by age 75 [49].

While the importance of screening for early detection of pancreatic cancer is recognized, there is no single ideal screening method. Annual endoscopic ultrasound or MRI with magnetic resonance cholangiopancreatography (MRCP) is commonly used. While endoscopic ultrasound is operator dependent, it has demonstrated a higher diagnostic yield in some studies [48]. While abdominal CT scans can be used, the sensitivity of this modality is lower than the others and there can be cumulative exposure to radiation when used in a screening program [50]. Patients should be encouraged to eliminate modifiable risk factors for pancreatic cancer including tobacco use and follow a low-fat diet [35].

References

1. Hall MJ, Forman AD, Pilarski R, Wiesner G, Giri VN. Gene panel testing for inherited cancer risk. J Natl Compr Cancer Netw. 2014;12(9):1339–46.
2. Vockley JG, Niederhuber JE. Diagnosis and treatment of cancer using genomics. BMJ. 2015;350:h1832.
3. Stoffel EM, Kastrinos F. Familial colorectal cancer, beyond Lynch syndrome. Clin Gastroenterol Hepatol. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2014;12(7):1059–68.
4. Network NCC. Nccn guidelines®. [May 18, 2018]; Available from: https://www.nccn.org/professionals/physician_gls/default.aspx.
5. ESMO. ESMO clinical practice guidelines. European Society for Medical Oncology; [May 18, 2018]; Available from: http://www.esmo.org/Guidelines.
6. Grover S, Kastrinos F, Steyerberg EW, Cook EF, Dewanwala A, Burbidge LA, et al. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA. 2012;308(5):485–92.
7. Guarinos C, Juarez M, Egoavil C, Rodriguez-Soler M, Perez-Carbonell L, Salas R, et al. Prevalence and characteristics of MUTYH-associated polyposis in patients with multiple adenomatous and serrated polyps. Clin Cancer Res. 2014;20(5):1158–68.
8. Borras E, Taggart MW, Lynch PM, Vilar E. Establishing a diagnostic road map for MUTYH-associated polyposis. Clin Cancer Res. 2014;20(5):1061–3.
9. Greenson JK, Huang SC, Herron C, Moreno V, Bonner JD, Tomsho LP, et al. Pathologic predictors of microsatellite instability in colorectal cancer. Am J Surg Pathol. 2009;33(1):126–33.
10. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol. 2010;7(3):153–62.
11. Bodo S, Colas C, Buhard O, Collura A, Tinat J, Lavoine N, et al. Diagnosis of constitutional mismatch repair-deficiency syndrome based on microsatellite instability and lymphocyte tolerance to methylating agents. Gastroenterology. 2015;149(4):1017–29 e1013.
12. Mork ME, Borras E, Taggart MW, Cuddy A, Bannon SA, You YN, et al. Identification of a novel PMS2 alteration c.505C>G (R169G) in trans with a PMS2 pathogenic mutation in a patient with constitutional mismatch repair deficiency. Familial Cancer. 2016;15(4):587–91.
13. Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet. 2014;51(6):355–65.
14. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Screening for the lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med. 2005;352(18):1851–60.
15. Pinol V, Castells A, Andreu M, Castellvi-Bel S, Alenda C, Llor X, et al. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA. 2005;293(16):1986–94.
16. Buchanan DD, Clendenning M, Rosty C, Eriksen SV, Walsh MD, Walters RJ, et al. Tumour testing to identify lynch syndrome in two australian colorectal cancer cohorts. J Gastroenterol Hepatol. 2016.
17. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol. 2005;23(3):609–18.
18. Yurgelun MB, Goel A, Hornick JL, Sen A, Turgeon DK, MTt R, et al. Microsatellite instability and DNA mismatch repair protein

deficiency in lynch syndrome colorectal polyps. Cancer Prev Res (Phila). 2012;5(4):574–82.
19. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96(4):261–8.
20. Dinh TA, Rosner BI, Atwood JC, Boland CR, Syngal S, Vasen HF, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res (Phila). 2011;4(1):9–22.
21. Kastrinos F, Stoffel EM. History, genetics, and strategies for cancer prevention in Lynch syndrome. Clin Gastroenterol Hepatol. [Historical Article Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2014;12(5):715–27; quiz e741–713.
22. Gryfe R, Kim H, Hsieh ET, Aronson MD, Holowaty EJ, Bull SB, et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. N Engl J Med. 2000;342(2):69–77.
23. Lynch HT, Kimberling W, Albano WA, Lynch JF, Biscone K, Schuelke GS, et al. Hereditary nonpolyposis colorectal cancer (Lynch syndromes I and II). I. Clinical description of resource. Cancer. 1985;56(4):934–8.
24. Sinicrope FA, Foster NR, Thibodeau SN, Marsoni S, Monges G, Labianca R, et al. DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy. J Natl Cancer Inst. 2011;103(11):863–75.
25. Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28(20):3219–26.
26. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the mosaic trial. J Clin Oncol. 2009;27(19):3109–16.
27. Andre T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the mosaic study. J Clin Oncol. 2015;33(35):4176–87.
28. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K, American Society of Clinical O. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2010;28(5):893–901.
29. Ratnayake P, Wakefield CE, Meiser B, Suthers G, Price MA, Duffy J, et al. An exploration of the communication preferences regarding genetic testing in individuals from families with identified breast/ovarian cancer mutations. Familial Cancer. 2011;10(1):97–105.
30. Dove-Edwin I, Sasieni P, Adams J, Thomas HJ. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ. 2005;331(7524):1047.
31. Choi YH, Briollais L, Win AK, Hopper J, Buchanan D, Jenkins M, et al. Modeling of successive cancer risks in Lynch syndrome families in the presence of competing risks using copulas. Biometrics. 2016.
32. Moller P, Seppala T, Bernstein I, Holinski-Feder E, Sala P, Evans DG, et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut. 2015.
33. Haanstra JF, Al-Toma A, Dekker E, Vanhoutvin SA, Nagengast FM, Mathus-Vliegen EM, et al. Prevalence of small-bowel neoplasia in Lynch syndrome assessed by video capsule endoscopy. Gut. 2015;64(10):1578–83.
34. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, et al. International cancer of the pancreas screening (caps) consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013;62(3):339–47.
35. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62; quiz 263.
36. Renkonen-Sinisalo L, Butzow R, Leminen A, Lehtovirta P, Mecklin JP, Jarvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer. 2007;120(4):821–4.
37. Nebgen DR, Lu KH, Rimes S, Keeler E, Broaddus R, Munsell MF, et al. Combined colonoscopy and endometrial biopsy cancer screening results in women with Lynch syndrome. Gynecol Oncol. 2014;135(1):85–9.
38. Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010;59(7):975–86.
39. Korsse SE, Harinck F, van Lier MG, Biermann K, Offerhaus GJ, Krak N, et al. Pancreatic cancer risk in Peutz-Jeghers syndrome patients: a large cohort study and implications for surveillance. J Med Genet. 2013;50(1):59–64.
40. Aytac E, Sulu B, Heald B, O'Malley M, LaGuardia L, Remzi FH, et al. Genotype-defined cancer risk in juvenile polyposis syndrome. Br J Surg. 2015;102(1):114–8.
41. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst. 1994;86(21):1600–8.
42. Vogelaar IP, van der Post RS, Bisseling TM, van Krieken JH, Ligtenberg MJ, Hoogerbrugge N. Familial gastric cancer: detection of a hereditary cause helps to understand its etiology. Hered Cancer Clin Pract. 2012;10(1):18.
43. Oliveira C, Senz J, Kaurah P, Pinheiro H, Sanges R, Haegert A, et al. Germline CDH1 deletions in hereditary diffuse gastric cancer families. Hum Mol Genet. 2009;18(9):1545–55.
44. Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. J Med Genet. 2010;47(7):436–44.
45. de Snoo FA, Bishop DT, Bergman W, van Leeuwen I, van der Drift C, van Nieuwpoort FA, et al. Increased risk of cancer other than melanoma in CDKN2A founder mutation (p16-Leiden)-positive melanoma families. Clin Cancer Res. 2008;14(21):7151–7.
46. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447–53.
47. Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009;302(16):1790–5.
48. Chang MC, Wong JM, Chang YT. Screening and early detection of pancreatic cancer in high risk population. World J Gastroenterol. 2014;20(9):2358–64.
49. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89(6):442–6.
50. Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology. 2012;142(4):796–804; quiz e714–795.

Molecular Diagnostics and Genomic Profiling in Individualized Therapies of Gastrointestinal Cancers

34

Mandana Kamgar and W. Michael Korn

Introduction

The human genome project, completed in 2003, provided the first reference map for the whole human genome and stimulated enormous advances in sequencing technology, making comprehensive genomic information readily accessible beyond basic science researchers. These technologies allowed for an increasingly detailed description of the molecular landscape of cancer, including gastrointestinal (GI) cancers, and were facilitated by large collaborative initiatives such as The Cancer Genomic Project (CGP) in the United Kingdom and The Cancer Genome Atlas (TCGA) project in the United States. Furthermore, widespread availability of next-generation sequencing (NGS) has led to extensive use of this method in the clinic and at the individual patient level.

The potential for clinical utility of cancer genomics is pronounced. In-depth molecular knowledge can offer unique opportunities for exploring cancer pathogenesis, germline mutation inheritance, and early cancer detection. NGS has the capability to identify unique features of an individual's cancer, hence the potential for personalizing diagnostic and therapeutic strategies. Monitoring a patient's cancer genome over time after receiving various lines of treatment has the potential to reveal underlying resistance mechanisms. This information, in turn, may lead to design of new treatments that overcome the resistance.

Despite the potential benefits, integration of cancer genomics in care delivery, especially in the area of solid cancer treatments, including gastrointestinal (GI) malignancies, has been challenging. This is largely due to complexity of cancer genomics. If cancer was a product of one prominent driver mutation or genetic aberration, design of drugs against that driver mutation/aberration would effectively control that cancer type. A prime example is Philadelphia chromosome positive chronic myelogenous leukemia (CML). Balanced chromosomal translocation between chromosome 9 and 22 leads to the formation of the BCR-ABL1 fusion gene. This results in expression of an abnormal protein with tyrosine kinase activity, leading to proliferation and survival advantage for cells harboring this translocation. Imatinib decreases the tyrosine kinase activity of the BCR-ABL protein or, in the case of gastrointestinal stromal tumors (GIST), the activity of the cKIT receptor tyrosine kinase. In contrast to CML, with few exceptions, GI cancers are mostly arising as a result of complex somatic mutations with involvement of multiple molecular pathways. Using therapies targeting one pathway therefore has not led to prolonged and clinically relevant control of GI cancers, as they rarely depend solely on activation of a single pathway. Furthermore, in presence of multiple mutations/genetic alterations it becomes difficult to identify the clinical importance of each mutation and prioritize treatment based on them. Temporal and spatial heterogeneity of the tumor, lack of availability of adequate tissue, limited access to clinical trials, and off-label treatments are all among challenges faced while utilizing clinical genomics in clinical practice.

Cancer Genomics Basics

Methodology

Next-generation sequencing (NGS) technologies have resulted in the most significant advances in cancer genomics and have revolutionized personalized medicine as we know it. These technologies allow for the entire genome or specific DNA segments to be sequenced at increased speed, accuracy, sensitivity, and drastically reduced costs compared to historic methods. Perhaps the most well-known NGS technology is sequence by

M. Kamgar
Department of Hematology Oncology, Karmanos Cancer Institute, Detroit, MI, USA

W. M. Korn (✉)
Caris Life Sciences, Phoenix, AZ, USA

Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA, USA
e-mail: wmkorn@carisls.com

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_34

synthesis (SBS), an approach that incorporates fluorescently labeled nucleotides into a DNA strand for visualization by emitting fluorophore signals [1]. Library preparation occurs when DNA is isolated from a specimen and undergoes fragmentation. Specialized adaptors are then ligated to each end of the DNA fragments, turning them into sequencing libraries. The sequencing libraries are then loaded into a flow cell where the adaptor fragments bind to surface-bound oligonucleotides. Amplification generates clonal clusters that are ready to be sequenced. Reversible terminator-bound deoxyribonucleotide triphosphates (dNTPs) are designed to match to complimentary bases during each sequencing cycle. Images are taken and a fluorescent signal corresponding to each base indicates that a nucleotide has been added. Lastly, data analysis aligns the sequences to a reference genome using bioinformatics software to identify any differences. Single nucleotide variations (SNVs), insertions/deletions (indels), and copy number variations (CNVs) detected from an individual sample highlight the clinical utility of NGS in oncology.

Genomic sequencing can be done in tumor tissue, adjacent normal tissue, and non-adjacent normal tissue (such as normal blood samples). Paired analyses of tumor and normal DNA allow for identification of harmless gene variants with significantly greater precision compared to tumor-alone analysis. Furthermore, this approach has been demonstrated to reveal germline mutations related to cancer predisposition syndromes frequently and in clinical situations where family history was not suggestive of an underlying genetic cause of cancer [2].

Beyond DNA sequencing, NGS of RNA is gaining increasing clinical relevance. This is, in part, based on the fact that messenger-RNA (mRNA) contains genomic information post RNA splicing (a process during which introns are removed and exons are joined to form the mature mRNA). This is of particular importance for the analysis of gene fusions, since chromosomal breakpoints are frequently located at various positions in intronic gene regions. These are easily missed by NGS gene panels due to incomplete coverage of the intronic regions but can be reliably identified at the RNA level, since the spliced RNA does not contain intronic sequences. RNA analysis can be accomplished by anchored multiplex polymerase chain reaction (PCR) followed by NGS or baited capture pull-downs. The latter is the current gold standard since anchored multiplex PCR is less sensitive. In addition, RNA sequencing using baited capture pull-down analysis allows for assessment of gene expression levels, thus providing information on increased gene expression as a result of gene amplification and on presence of RNA form mutant alleles. This is important for the interpretation of mutations, since it is known that about 30% of gene mutants are not expressed [3]. Lastly, advanced analysis approaches allow for detection of Human Leukocyte Antigen (HLA) subtypes and Homologous recombination deficiency (HRD), both features of immediate clinical relevance.

Principles of NGS-Based Clinical Decision-Making in Gastrointestinal Oncology

Direct Targeting of Activated Oncogenes

Among GI cancers/tumors, advances in the treatment of gastrointestinal stromal tumors (GIST) demonstrate how cancer genomics can reveal crucial information, allowing for the design of disease-specific treatment approaches. Unlike most GI tumors, these rare tumors are believed to be derived from the interstitial cells of Cajal [4]. These tumors are highly unresponsive to chemotherapy and radiation. Surgical resection can temporarily control the disease, albeit many will relapse eventually [5]. Genomic studies have revealed that gain of function mutations in the KIT (~80%) and platelet derived growth factor (PDGFR) genes (~10%) are drivers of tumor growth in the majority of GISTs [6]. Activating mutations in these oncogenes result in production of receptors with constitutively active tyrosine kinase activity, hence activation of downstream pathways and survival advantage of affected cells [7]. Highly specific and potent tyrosine kinase inhibitors such as imatinib can potently inhibit activated pathways resulting in cell killing [8]. Treatment with imatinib induces objective response rates of up to 50–75% with a subset of patients reaching durable response [9]. Genotyping of GIST has implications for the choice of treatment and dosage of the treatment applied. For example, while GIST tumors with KIT exon 11 mutations are mostly sensitive to imatinib doses of 400 mg/day, those with KIT exon 9 mutations are less sensitive to imatinib and may require higher doses (800 mg/day). Presence of a KIT exon 17 (D816V) mutation implies resistance to imatinib as does a PDGFRA exon 18 mutation (D842V) [10]. Genotyping is therefore now a standard part of GIST treatment, whenever use of tyrosine kinases is considered.

Targeting Molecular Themes That Span Across Disease Types

Unlike GIST, the majority of GI cancers are products of complex genomic and epigenetic changes, and many of these are specific to individual cancer types. However, genomic studies have revealed alterations that are shared across GI and non-GI cancers and can be exploited across tumor types. Occurrence of certain fusion genes and alterations in DNA repair pathways demonstrate the potential of cancer-type-independent, purely molecularly driven treatment approaches.

Gene Fusions

Genomic translocations involving kinases can lead to formation of chimeric proteins with constitutively activated kinase function and oncogenic potential. A prominent example of this mechanism of oncogene activation are gene fusions involving the tropomyosin receptor kinase (Trk) family that

encode for three transmembrane tyrosine kinase proteins (NTRK1–3). Trks play a major role in development and function of neuronal tissues [11]. Pathogenic NTRK gene fusions result in constitutively active kinases and are found in 0.5–2.7% of colorectal cancers [12–14] and ~3% of intrahepatic cholangiocarcinomas [15] and also found rarely, but repetitively, in gastric and pancreatic cancers [16]. Larotrectinib was approved by the US Food and Drug Administration (FDA) for use in any tumor type harboring such gene fusions in November 2018 based on an overall response rate of 75%. Entrectinib and LOXO-195 are examples of TRK inhibitors with promising results in early-phase trials, with occasional durable responses lasting beyond 2 years [17–19]. NTRK, ROS, and anaplastic lymphoma kinase (ALK) rearrangements in GI cancers can be efficiently evaluated by a two-step immunohistochemistry/polymerase chain reaction (IHC/PCR) method [16] or through RNA sequencing.

Mismatch Repair (MMR)

Genomic evaluation of patients with Lynch syndrome revealed defective DNA mismatch repair (MMR) as the pathogenic mechanism predisposing the affected patients to different cancers, including colorectal and endometrial cancer [20]. MMR is a DNA repair mechanism that identifies DNA base mismatches and abnormal DNA loops formed during DNA replication, recombination, and repair and corrects these errors [21]. MMR deficiency (MMR-D) in Lynch syndrome is mostly due to loss of function mutation in mutL homologue 1 (MLH1), mutS homologue 2 (MSH2), MSH6, or post meiotic segregation increased 2 (PMS2) [22]. Loss of any of these proteins results in microsatellite instability. Microsatellites are small repetitive sequences of DNA, different among individuals but highly preserved during the lifespan of one individual [23]. Patients with MMR-D are susceptible to somatic mutations resulting in variations of length of microsatellites, a status called microsatellite instability (MSI-H), and to the development of mutations in large numbers of genes harboring longer stretches of a single nucleotide, such as adenosine. Detection of MMR-D is currently accomplished by IHC evaluation of expression of MMR-D-related proteins (MLH1, MSH2, MSH5, and PMS2) or DNA-based evaluation for microsatellite instability. Not every tumor with MSI-H phenotype harbors the genetic mutations mentioned [21]. Genomic and epigenetic evaluation has shown presence of MMR-D beyond Lynch syndrome. For example, CpG island methylation is a common mechanism for silencing of genes, including tumor suppressor genes [24]. Hypermethylation of the MLH1 gene is a common mechanism for MMR-D in colorectal cancer [25]. MicroRNAs (miRNAs) are non-coding RNAs involved in epigenetic control of multiple human genes. miRNA-155 is overexpressed in MSI-H colorectal tumors [26] and is proposed to silence MMR genes and lead to MMR-D phenotype. Moreover, there are MSI-H tumors for which no specific mutation/epigenetic change linked to MMR-D is described yet.

Regardless of the pathogenesis, the high number of mutations present in MSI-H tumors leads to a high rate of expression of immunogenic neoantigens (proteins specifically expressed in the tumor cells and recognized by the immune system as "foreign"). Expression of these neoantigens promotes susceptibility of cancers with MMR-D to immunotherapy [27, 28]. Clinical trials have established the role of immune checkpoint inhibitors, such as the programmed cell death protein 1 (PD-1) inhibitors pembrolizumab and nivolumab [29, 30].

DNA Double-Strand Repair (DDR)

While Lynch syndrome provided the clinical background for the exploration of mismatch repair, hereditary breast and ovarian cancer syndromes revealed a critical role of mutations in the Breast cancer 1/2 (BRCA 1/2) genes. Both genes are key components of the enzymatic machinery involved in repairing DNA double-strand breaks by homologous recombination (HR). Since maintenance of DNA integrity is crucial for cellular survival, redundant mechanisms exist. BRCA proteins play a major role in DNA double-strand repair (DDR) through the HR pathway. In cells with deficient HR, double-strand damage repair relies on non-homologous end joining (NHEJ). This mechanism is error-prone with a possibility of accrual of deletions or small insertions. Therefore, cells deficient in BRCA1/2 are prone to accumulate DNA errors and genomic instability overtime resulting in increased risk of malignant transformation [31]. A key feature of cells harboring HR mutations resulting in HR deficiency is the finding of genome-wide loss of heterozygosity—a phenomenon that is increasingly used to detect functional HR deficiency [32, 33]. It is noteworthy that HR is a complex mechanism and relies on multiple enzymes. Ataxia telangiectasia mutated (ATM), ATM and rad3-related (ATR), partner and localizer of BRCA2 (PALB2), checkpoint kinase 2 (CHEK2), and an additional ~30 enzymes are needed to carry out HR flawlessly. Mutations in genes encoding for such proteins are increasingly recognized to cause HR deficiency beyond alterations in BRCA1/2—a phenomenon known as BRCAness [34].

Pivotal work performed by the Ashworth and Helleday groups demonstrated that mutations in BRCA1/2 and cells with BRCAness features can be targeted through induction of synthetic lethality [35, 36]. This concept was initially described in yeast genetics and used to uncover compensatory pathways. It is based on the presence of at least two genes that are crucial for cell survival and are able to compensate for loss of the other. Inactivation of one such gene will not lead to cell death, as the compensating gene covers

for the lack of function resulting from loss of the second gene. However, defects in both can lead to cell death, hence synthetic lethality. Poly ADP-ribose polymerase 1 (PARP1) and BRCA display such behavior. PARP1 is responsible for recognition and repair of single-stranded DNA breaks. If PARP function is deficient, these single-strand breaks can turn to double-strand breaks during DNA replication and can be repaired by HR. Cells carrying BRCA1/2 mutations or the BRCAness molecular feature therefore are susceptible to PARP inhibition. While somatic mutations in BRCA1/2 normally lead to mono-allelic loss of BRCA1/2 in tumors, germline carriers of BRCA1/2 mutations are susceptible to bi-allelic loss of wild-type BRCA genes. This is due to frequent occurrence of locus-specific loss of heterozygosity in tumors of germline carriers of BRCA1/2 mutation. Such tumors are exquisitely susceptible to PARP inhibition [37, 38]. The role of PARP inhibition in advanced cancer (including breast, ovarian, prostate and pancreas cancer) with germline BRCA mutation was evaluated in a phase II trial [39]. Single-agent olaparib led to an overall response rate of 26% and disease stabilization lasting more than 8 weeks in 42% of patients. Multiple clinical trials are ongoing to evaluate the clinical utility of PARP inhibition in the context of germline BRCA mutation, and more importantly, BRCAness (examples: NCT02184195, NTC02677038). ATM, ATR, and CHEK1/2 are also genes with potential synthetic lethality in the context of BRCA mutation [40]. Efficacy of direct CHEK 1 inhibitor prexasertib in patients with advanced tumor and homologous repair deficiency is being evaluated in a phase II ongoing clinical trial (NCT02873975).

Matching Treatments and Molecular Abnormalities

Direct Targeting of Mutant Proteins

Availability of genomic evaluation at an individual level has brought the goal of rationally matching treatments and individual patients in reach, and an increasing number of patients with gastrointestinal malignancies might benefit from genomic sequencing. Multiple large-scale clinical trials are ongoing to explore the role of molecularly matched treatments. The multi-arm multi-stage FOCUS4 trial is a biomarker-stratified prospective study open to patients with metastatic colorectal cancer fit for first-line chemotherapy in the UK [41]. Eligible patients are started on 16 weeks of standard chemotherapy, during which the molecular characteristics of the tumor is delineated. In the second part, responders to chemotherapy are stratified to cohorts of biomarker directed "maintenance" targeted therapy or treatment with a placebo. If promising signals of clinical activity are seen, then the cohort is expanded into a phase III clinical trial. The Targeted Agent and Profiling Utilization Registry (TAPUR) study, launched by the American Society of Clinical Oncology (ASCO), is a phase II clinical trial with a direct matched treatment design. So far, 16 arms have been established with different targeted therapies being associated with each arm (NCT02693535). The National Cancer Institute-Molecular Analysis of Therapy Choice (NCI-MATCH) trial is a phase II study aiming to explore the efficacy and safety of genetic testing-directed therapy in lymphomas, multiple myelomas, and solid tumors. As of February 2018, this study had 30 arms with intended use of 23 distinct drugs. This study also aims to search for possible mechanisms of resistance and predictive biomarkers (NCT02465060).

Exploiting Cancer Cell Vulnerabilities Through Induction of Synthetic Lethality

This strategy mainly relies on finding weaknesses in tumor cells and trying to apply treatments that take advantage of this weakness. Application of treatments with potential for inducing DNA damage to tumors with defective DNA damage repair mechanisms is one such utility of cancer genomics. Platinum-based agents are believed to exert their cytotoxic effect by DNA damage. Agents known to impair DNA repair mechanism including PARP inhibitors are therefore combined with platinum-based chemotherapy to enhance the cytotoxicity and lethality on cancer cells. Apply this to a cell with already damaged DNA repair (such as cells with BRCAness) and potentially you will have even more effective cancer lethality. Combinations of inhibitors of ATM, ATR, PARP, WEE1, CHEK1/2, and platinum-based agents are the subjects of study in multiple clinical trials [42].

Role of Next-Generation DNA Sequencing as a Diagnostic Tool

Genomic profiling not only has the potential to guide therapies, but also adds to the armamentarium of cancer diagnostics. The use of molecular profiling technologies to identify the tissue of origin in carcinomas of unknown primary (CUP) highlights this aspect. CUP comprises a heterogeneous mixture of cancers. These tumors share presence of metastatic disease without an identifiable primary tumor after completion of standardized/adequate diagnostic workup. The diagnostic workup traditionally has consisted of imaging and immunohistochemical studies of the tissue biopsy [43]. Application of molecular profiling has opened new potentials in recognizing the primary source of CUP. As an example, in a prospective trial, using a 92-gene reverse transcription (RT)-PCR assay in 289 CUP samples resulted in prediction of tissue of origin in 85% of tested tumors. It was suggested that application of site-specific treatments might translate to better clinical outcomes [44]. Among the most frequent predicted primary sites were biliary tract (18%) and colorectal (10%) cancers. Inclusion of liquid biopsy and evaluation of

circulating tumor DNA (ctDNA) or circulation tumor cell (CTCs) might further enhance ability to define the tissue of origin and search for driver actionable mutations [45]. Further prospective studies are needed to establish the diagnostic role and therapeutic utility of molecular profiling in CUP.

Germline Evaluation

Lynch syndrome and BRCA1/2 are examples of utility of genomic sequencing in germline evaluation. Germline evaluation at an individual level can identify cancer susceptibility mutations and set the stage for enrollment in intensified screening/preventive protocols of affected individuals and their relatives. Furthermore, germline evaluation can add valuable knowledge to pathogenesis of cancer and bring new therapeutic options to the clinic. So far, such examples have been discussed above in the context of hereditary breast and ovarian cancer (HBOC) and Lynch syndrome. Another example of increasing clinical importance is the increasing recognition of genetic underpinnings of pancreas cancer. Other than HBOC and Lynch syndrome, family members affected by familial melanoma (FM), familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), and Li-Fraumeni syndrome (LFS) are also at increased risk of development of pancreatic adenocarcinoma [46]. Germline sequencing of patients with pancreatic cancers has revealed mutations in pancreatic adenocarcinoma development: BRCA1/2, PALB2, ATM, cyclin-dependent kinase inhibitor 2A (CDKN2A; role in FM), MLH1/2, MSH6, PMS2, epithelial cell adhesion molecule (EPCAM; role in Lynch), adenomatous polyposis coli (APC), serine-threonine kinase 11 (STK11; role in PJS), protease serine 1 (PRSS1; role in hereditary pancreatitis), and tumor protein 53 (TP53; role in Li-Fraumeni) [47].

GI and pancreaticobiliary neuroendocrine tumors can also develop in the context of hereditary syndromes. Multiple endocrine neoplasia type 1 (MEN1), Von Hippel-Lindau (VHL), neurofibromatosis 1 (NF-1), and tuberous sclerosis complex (TSC) are all autosomal-dominated syndromes resulting in increased risk of GI and pancreaticobiliary neuroendocrine tumors [48].

Gastric cancer is mostly a sporadic disease, with 1–3% of cases occurring in the context of hereditary syndromes. Hereditary diffuse gastric cancer (HDGC) is a well-recognized form of hereditary gastric cancer. Individuals with germline pathogenic E-cadherin gene (CDH1) mutation are at increased risk of both lobular breast cancer and diffuse-type gastric cancer. Pathogenic germline mutations in CDH1, however, are found in only 40% of families that would clinically qualify as HDGC. Genomic studies have revealed mutations in multiple other genes as culprits for development of HDGC; most of these mutations are reported only in single families [49].

Understanding Genomic Features Resulting in Exceptional Therapeutic Responses.

The discovery of MMR deficiency as a predictive biomarker of response to immunotherapy in colorectal cancer highlights the utility of cancer genomic sequencing in patients showing exceptional responses to therapies. A phase I study for evaluation of safety of immunotherapy with checkpoint inhibitor in advanced solid tumors showed exceptional response in one patient with CRC [50, 51]. Genomic evaluation of this patient showed mismatch repair deficiency (MMR-D; MSI-H genotype). Based on the hypothesis that mismatch repair deficiency might relay tumor susceptibility to immune checkpoint inhibitors, a phase II study was designed [29]. This study showed significantly an improved response rate and progression-free survival in the MMR-D CRC cohort as opposed to the mismatch proficient CRC group. Data for non-CRC cohort with MMR-D, published later, demonstrated profound sensitivity to PD-L1 inhibition in MMR-D cancers across tumor types [28] and led to US FDA approval of pembrolizumab for advanced solid tumors with MMR-D. Nivolumab has also gained FDA approval in advanced colorectal cancer with MMR-D, pending further prospective trials [30].

Gastrointestinal Cancer Genomics by Tumor Site

An ever-growing body of genomics data on molecular features of gastrointestinal cancers has helped to identify recurrent molecular features that subdivide classical histologic types of gastrointestinal cancers. These increasingly inform clinical science and set the stage for the development of rational treatment strategies. We will review key findings and discuss clinical implications:

Esophageal/Gastric Cancer

Molecular Classification

While distinct clinical features of squamous and adenocarcinomas of the esophagus have long been observed, a recent TCGA study of esophageal cancers established molecular distinctions between the two subtypes. The squamous cell histology resembled squamous cell carcinomas (SCCs) of other organs rather than adenocarcinoma of the same organ. Three SCC subtypes were identified in this study. Subtype 1 had frequent alterations in NRF2 pathway (which regulates response to oxidative stressors) and amplifications of SOX2 and TP63. Gene expression of this subtype resembled that of classical lung SCC and head and neck SCC. Subtype 2 had high leukocyte infiltration, higher expression of immunomodulatory protein BST-2, and high level of cleaved

caspase-7. This indicates a possible role for immune-directed and apoptosis-regulating therapies in this subtype of SCC. Subtype 3, comprising only a minority of esophageal SCCs (4 tumors), had relatively low TP53 mutations (25%) but frequent alterations of PI3K (100%) and mixed-lineage leukemia protein 2 (MLL2) (75%) pathways. Adenocarcinomas of the esophagus, on the other hand, had much in common with the chromosomally unstable variant of gastric adenocarcinoma with ERBB2/HER2 and vascular endothelial growth factor A (VEGFA) amplification and TP53 mutation [52].

TCGA results of gastric cancer were published in 2014 [53]. Based on comprehensive molecular evaluation of 295 samples, 4 major tumor subtypes were identified. Epstein-Barr virus (EBV)-associated tumors (9%) were rich in DNA methylation (lacking the MLH1 hypermethylation though) and had frequent PI3K mutations (80%) and high amplifications of JAK-1 and PD-L1. MSI-H tumors (22%) were characterized by high mutational burden. The remainder of cases was classified by degree of aneuploidy as genomically stable (20%) and chromosomally instable (50%) tumors. Genomically stable tumors carry the highest percentage of CDH1 mutation. This gene encodes for a calcium-dependent cell-cell adhesion glycoprotein (E-cadherin). Lack of expression of E-cadherin leads to production of tumors that do not form solid masses, but rather form sheets of cancerous cells beneath the stomach lining, hence the term "diffuse gastric cancer." The chromosomally instable (CIN) subtype demonstrates a high degree of aneuploidy, high percentage of P53 mutation, and amplifications of receptor tyrosine kinases. While EBV-associated tumors were mostly located in the fundus and body of the stomach, CIN tumors were localized in the gastroesophageal junction (GEJ) or the cardia of stomach.

The Asian Cancer Research Group (ACRG) performed a genomic analysis of 300 gastric adenocarcinoma samples obtained from a single center in South Korea [54]. Whole-exome sequencing of the samples revealed four different subtypes: MSI-H (22%), microsatellite-stable/epithelial-to-mesenchymal transition (MSS/EMT:15%), MSS/TP53+ (26%), and MSS/TP53- (35%). Linking the subtypes to clinical outcome, this classification was of prognostic value in terms of overall survival: MSI-H > MSS/TP53+ > MSS/TP53− > MSS/EMT. MSS/TP53− had higher percentage of human epidermal growth factor receptor 2 (HER2) amplification (17.4 as opposed to <3% in other groups). Compared to all other groups, the MSI-H subtype had significantly higher ARID1A (44%), PI3K-PTEN-mTOR (42%), ALK (16%), ERBB2, and KRAS (16%) somatic mutations. The MSS/TP53+ had the highest percentage of EBV-associated tumors. The MSS/EMT was found in patients with younger age and the majority of patients had diffuse-type gastric cancer. Prognostic value of the classification system is verified in independent cohorts [54].

Clinical Utility of Molecular Analysis in Esophagogastric Cancer

Immune Checkpoint Inhibitors

Both the ACRC and TCGA analyses demonstrated that 22% of gastric cancers are mismatch-deficient. MMR status and PD-L1 expression both can serve as predictive biomarkers for response to immune checkpoint inhibitors. Using PD-L1 as predictive of response to treatment, phase I/II gastric cancer studies demonstrated response rates to pembrolizumab and nivolumab treatment ranging from 16% to 22% [55, 56]. KeyNote-059 was a phase I study of pembrolizumab in patients with advanced gastric/GEJ tumors. Of participants in this study, 55% had positive PD-L1 expression by IHC (≥1%). The objective response rate in PD-L1 expressers with unknown MMR status or MSS status was reported as 13.3%. Nearly 60% of patients with a response had response duration more than 6 months. This study led to FDA approval of pembrolizumab for patients with advanced gastric/GEJ adenocarcinomas with ≥1% expression of PD-L1 by IHC (NCT02335411). Among the patients enrolled in this study only 3% (7 patients) had MSI-H tumors. Response rate to pembrolizumab among these patients was 57%. The aforementioned study of pembrolizumab in MMR-D advanced solid tumors also included five gastroesophageal cancers, three of which had complete response to treatment (60%) [28]. Based on the results of this study, pembrolizumab is approved by the FDA for advanced solid cancers in general with MMR-D status—this includes gastric and GEJ tumors.

HER2 Inhibitors

HER2 was the first widely accepted biomarker for personalized treatment of gastric cancer. Around 12–20% of US patients with gastric/GEJ tumors are estimated to have HER2 overexpression and/or amplification, as determined by IHC or fluorescence in situ hybridization (FISH), respectively [57, 58]. Treatment with trastuzumab (a monoclonal antibody directed against HER2) along with chemotherapy as first-line therapy in patients with HER2 over-expressing/amplified gastric cancer improves response rates and overall survival compared to chemotherapy alone [59]. HER2 amplification can be determined reliably by next-generation DNA sequencing. Addition of pertuzumab (another monoclonal antibody against HER2) to trastuzumab for first-line treatment of HER2-positive gastric/GEJ was shown to be well tolerated in a phase II study [60]. A phase III trial (NCT01774786) exploring the potential of this combination did not show overall survival benefit as presented to the European Society for Medical Oncology (ESMO) in 2017 [61]. The utility of TDM-1 (HER2/chemotherapy drug conjugate) in addition to chemotherapy in gastric cancer was evaluated in a phase I trial (NCT01702558), which showed

fair tolerance of the drug. However, the GATSBY trial, a phase II/III trial comparing TDM-1 to taxane-based chemotherapy in advanced HER2-positive gastric cancer (NCT01641939), was terminated due to futility.

Some gastric cancers harbor activating HER2 mutations. Neratinib is an oral irreversible HER2 tyrosine kinase inhibitor. SUMMIT, a phase II basket trial, evaluated the efficacy of neratinib in treatment of solid tumors with HER2 activating mutations, including gastric/GEJ tumors. While occasional responses were seen in biliary cancer, gastric and colorectal cancers did not have significant durable response to this treatment [62].

Vascular Endothelial Growth Factor Receptor Blockade

VEGF overexpression as determined by IHC is a common finding in gastric/GEJ tumors (~60%) [63]. In agreement with this, the TCGA dataset demonstrates recurrent amplification of the gene encoding VEGFA in gastric cancer, especially for the CIN subtype. Ramucirumab, a VEGF receptor-2 (VEGFR2) antibody, with or without paclitaxel is approved for second-line treatment of gastric/GEJ cancer after progression on chemotherapy [64, 65]. Ramucirumab has been tested in the first-line setting in combination with capecitabine/cisplatin (phase III RAINFALL study). Although combination improved progression-free survival, no significant overall survival benefit was added with this combination [66]. VEGF expression level has not been successfully established as a biomarker of response to VEGF inhibitors. Identification of a predictive biomarker of response/resistance to VEGF inhibition is therefore urgently needed.

Fibroblast Growth Factor Receptor 2 Inhibitors

Fibroblast growth factor receptor 2 (FGFR2) gene encodes the FGFR2 tyrosine kinase. This protein plays an important role in cell proliferation and angiogenesis. FGFR2 amplification has been reported in around 15% of diffuse-type gastric cancers [67]. AZD4547 (FGFR2 inhibitor) has been tested as a single agent in advanced gastric cancer with FGFR2 amplification. Compared to paclitaxel, AZD4547 was not associated with improvement in survival [68]. The role of dovitinib (a multikinase inhibitor against FGFR, VEGFR, PDGFR, FLT-3, KIT, CSF1) +/− chemotherapy in advanced gastric cancer patients with FGFR2 amplification is under active investigation (NCT01719549, NCT01921673). Initial studies of the anti-FGFR2b antibody FPA-144 showed promising results [69]. A combination study with chemotherapy is currently ongoing (NCT03343301).

PI3K-AKT-mTOR Inhibitors

As demonstrated in the TCGA study, the PI3K-AKT-mTOR pathway is frequently affected in gastric cancer. Combination of PI3K inhibitors with other targeted treatments for advanced solid tumors is being studied in early-phase clinical trials (NCT01613950, NCT01576666). AZD5363 and GDC-0068 are examples of AKT inhibitors, the role of which in combination with chemotherapy is under study for treatment of gastric cancer (NCT02451956, NCT02449655, NCT01896531). Everolimus (mTOR inhibitor) as a single agent in advanced gastric cancer has not been proven to lead to improved overall survival compared to placebo [70], although exceptional responders were observed in cases with multiple molecular alterations within the pathway [71].

Small Bowel Adenocarcinoma

Molecular Classification

Small bowel adenocarcinoma (SBA) is a relatively rare type of GI malignancy. Currently, this disease is treated in analogy to the treatment of colorectal cancer (CRC). However, when compared to CRC stage by stage, SBA is generally associated with worse outcome [72]. A recent study showed distinct genomic features of SBA compared to CRC [73]. Most frequent mutations in SBA were TP53 (58%), KRAS (54%), APC (27%), SMAD4 (17%), and PI3K (16%). Compared to CRC, APC and TP53 mutations were less frequent in SBA, whereas CDKN2A was more frequent in SBA (14% vs 3%). There were frequent potentially targetable mutations in SBA as shown in Table 34.1.

Among SBA tumors, 7.6% were MSI-H and 7.9% were MMR-D by IHC. Nearly 10% of SBAs had high mutational burden. These features suggest a potential role for immunotherapy in SBA.

Table 34.1 The most common potentially targetable mutations in SBA

Gene	Mutation rate (%)
PI3K	16
HER2	9.5
BRAF	9.1
ATM	7.6
FBXW7	6.9
ERBB3	6.3
NF1	6.0
CTNNB1	5.7
MDM2	5.7
PTEN	5.7

PI3K phosphoinositide 3-kinase, *HER2* human epidermal growth factor receptor 2, *ATM* ataxia telangiectasia mutated, *FBXW7* F-box/W 7, *NF1* neurofibromatosis type 1, *CTNNB1* catenin beta 1, *MDM2* mouse double minute 2, *PTEN* phosphatase and tensin

Colorectal Cancer

Molecular Classification

TCGA data on colorectal cancer (CRC) sequencing were published in 2012 [74]. The analysis identified 24 significantly mutated genes with APC, TP53, SMAD4, KRAS, and PIK3CA being among the most frequently mutated genes. Among samples evaluated as part of the TCGA colorectal cancer analysis, 16% were hypermutated, of which 75% had high microsatellite instability (MSI-H) and the rest had somatic mutations in one or more of mismatch repair genes.

Mutation frequencies were significantly different among hypermutated versus non-hypermutation tumors, as stated in Table 34.2.

Other molecular classification systems for CRC have been proposed previously by different groups [75, 76]. Results of the CALGB 80405, CRYSTAL, and FIRE-3 studies highlighted that right- and left-sided colon cancers demonstrate distinct clinical behaviors [77, 78]. This might be explained by the difference in the embryological origin of right colon (midgut) versus left colon (hindgut). In agreement with this, genomic studies have established multiple molecular differences between the two. Right-sided lesions are frequently hypermutated, MSI-H, show immune infiltration, and carry BRAF mutations [79]. High frequency in BRAF mutation in right-sided tumors is associated with high CpG island methylation phenotype (CIMP). CIMP-associated methylation of MLH1 promoter is the predominant cause of MSI-H status in these tumors [80]. Left-sided tumors on the other side are mostly MSS tumors with epidermal growth factor receptor (EGFR) amplification/overexpression, WNT/MYC pathway activation, and TP53 mutation [81]. It is therefore not surprising to see differences in response to treatments including EGFR inhibitors based on the sidedness of the tumor.

Table 34.2 The most frequent mutations in colorectal cancer (CRC) by mutational burden

Hypermutated CRC (%)	Non-hypermutated CRC (%)
ACVR2A (63)	APC (81)
APC (51)	TP53 (60)
TGFBR2 (51)	KRAS (43)
BRAF (46)	TTN (31)
MSH3 (40)	PI3K (18)
MSH6 (40)	SMAD4 (10)

ACRV2A activin a receptor type 2A, *APC* adenomatous polyposis coli, *TGFBR2* transforming growth factor beta receptor 2, *BRAF* B-Raf, *MSH3* mutS homologue 3, *MSH6* mutS homologue 6, *TP53* tumor protein 53, *KRAS* Kirsten rat sarcoma, *TTN* Titin, *PI3K* phosphoinositide 3-kinase, *SMAD4* Mother Against DPP homolog 4

Clinical Utility

WNT Signaling

Uninhibited Wnt signaling is the hallmark of colorectal carcinogenesis and tumor maintenance. Adenomatous polyposis coli (APC) gene is mutated in the majority of colorectal cancers (~50–80%). Biallelic inactivating mutations of APC gene, a tumor suppression gene, lead to decreased production of APC protein. This in turn leads to uninhibited activation of the β(beta)-catenin-dependent Wnt signaling [82]. APC mutation is not the only mechanism for uninhibited Wnt signaling. Mutations in the Wnt gene itself or regulators of Wnt signaling other than APC also can lead to the same uninhibited signaling cascade activation: APC 50%, FBXW7 10%, β(beta)-catenin 5%, TCF7L2 4%, and AXIN1 3.5% [83]. Furthermore, epigenetic dysregulation can lead to overexpression or lack of expression of these genes and serve as another mechanism of aberrant Wnt signaling in colorectal cancer. Therapeutic inhibition of Wnt signaling has therefore been a long-standing goal [84]. However, development of specific and potent inhibitors of this pathway has been challenging. Wnt signaling plays a major role in regeneration of intestinal stem cells and maintenance of healthy intestinal tissue. Therefore, effective inhibition of this pathway may lead to severe GI toxicity. Wnt signaling is interconnected with various additional signaling circuits. Thus, effects of inhibition of this cascade can be counteracted by activation compensatory pathways. Despite the early disappointment, work on inhibitors of this pathway is still ongoing without a clearly promising compound having emerged [85].

BRAF Mutation

RAS-RAF-MEK-ERK signaling plays a major role in cell growth, differentiation, and survival. Activating mutations of BRAF oncogene are found in nearly 10% of colorectal cancers, in particular in the form of BRAF V600E mutations. This mutation is associated with poor prognosis and lack of response to conventional chemotherapy. Unlike melanoma, application of single-agent BRAF inhibitors in BRAF-mutant colorectal cancer has been ineffective so far. Feedback activation of EGFR pathway is proposed as one reason for ineffectiveness of vemurafenib (a BRAF inhibitor) in colorectal cancer. Combination of EGFR inhibition and BRAF inhibition is therefore suggested as a mechanism to overcome such resistance [86]. Addition of vemurafenib to irinotecan and cetuximab has been evaluated in a phase II clinical trial, and initial results presented at the ASCO annual meeting in 2017 suggested improved progression-free survival [87]. BGB283, a dual EGFR and BRAF inhibitor, has shown effective anti-tumor activity in preclinical models of BRAF-mutated colorectal cancer [88] and is under evaluation in solid tumors with BRAF mutation (NCT02610361).

Triple inhibition of BRAF, EGFR, and MEK also has been studied with promising results [89–91]. Triplet inhibition with BRAF, EGFR and MEK inhibitors is now recommended by the National Comprehensive Cancer Network (NCCN) for colorectal patients with BRAF V600E mutation [92].

HER2 Amplification

HER2 amplification can be found in around 5% of RAS wild-type colorectal cancers. HERACLES-A, a phase II clinical trial performed in Italy, demonstrated effectiveness of lapatinib (a HER-family tyrosine kinase inhibitor) in combination with trastuzumab (monoclonal anti-HER2 antibody) in heavily pretreated metastatic colorectal cancer patients with positive HER2 expression (by IHC) or gene amplification (FISH) [93].

Rare Mutations

MMR Status MMR status as a predictive biomarker for response to immunotherapy in metastatic colorectal cancer has been discussed previously in this chapter. The role of MMR status as predictive of response to checkpoint inhibitors in the adjuvant setting is currently under evaluation (NCT02912559). MMR-D status has been proposed as predictive of lack of response to adjuvant 5-fluorouracil (5-FU)-based chemotherapy in patients with early-stage colon cancer [94, 95]. Other than a role as a predictive biomarker, MMR-D can serve as a prognostic biomarker in colorectal cancer of different stages, especially stage II colon cancer [96–99]. Based on these studies, adjuvant chemotherapy is not recommended with CRC patients with stage II and low-risk features carrying mismatch repair deficiency.

NTRK Gene Fusions Universal use of NGS has led to detection of rare, but recurring mutations/gene alteration. These mutations at times serve as predictive biomarkers for targeted therapy. Neurotrophic tropomyosin receptor kinase (NTRK) gene fusion is one such rearrangement that is found in colorectal cancer (~0.5–2.7%). Availability of TRK inhibitors has attracted attention to these gene fusions as target of therapy. Larotrectinib is a TRK inhibitor with promising results in phase I/II trials in pediatrics and adults with advanced solid tumors with NTRK gene fusions, with occasional durable responses [18]. Entrectinib (a pan-TRK, ROS-1, and ALK inhibitor) was proven safe in two phase I clinical trials among patients with various metastatic solid tumors including colorectal cancer [17]. Efficacy of entrectinib is being further evaluated in a phase II trial (STARTRK-2) (NCT02568267). LOXO-195 (a second-generation TRK inhibitor) is being studied in early-phase clinical trials (NCT03215511). Overall tolerability and durability of response among responders to the aforementioned inhibitors highlight the therapeutic potential of these inhibitors. Very recently, data became available demonstrating co-occurrence of mismatch repair deficiency and NTRK gene fusions. The underlying biology remains unclear and optimal therapeutic sequencing of NTRK inhibitors and immune checkpoint inhibitors needs to be determined.

Other than the therapeutic purpose, rare mutations can at times serve as biomarkers for the presence of hereditary colorectal cancer. Biallelic mutations of MUTYH are found in around 1% of patients with colorectal cancer. It is associated with a pseudo-polyposis phenotype and a 28-fold increase in CRC risk [100]. Germline mutation of MUTYH gene leads to defective base excision repair (BER) and accumulation of mutations in other genes, and eventually cancer development. Detection of such mutations by NGS can lead to improved surveillance and therefore improved outcome in families with such germline mutations.

EGFR Inhibition

EGFR monoclonal antibodies have an established role in the treatment of metastatic colorectal cancer. In 2006, it was revealed that a mutation in exon 1 of KRAS is related to resistance to cetuximab [101]. Later in 2013, as part of the PRIME clinical trial, the predictive role of extended RAS mutation (KRAS and NRAS exon 2, 3, and 4) was established, this time in response to panitumumab [102]. Routine assessment for extended RAS mutations is now a standard of care step before initiation of treatment with EGFR monoclonal antibodies. Debate is ongoing about how much BRAF serves as a predictive biomarker or response to EGFR antibodies, on top of its role as a poor prognostic biomarker in general. A meta-analysis of nine phase III and one phase II trials, evaluating the role of cetuximab/panitumumab either as first- or second-line treatment, suggested no benefit from treatment with either one in carriers of exon 15 BRAF mutation [103]. One study presented at the 2015 ASCO annual meeting suggested systematic BRAF mutation analysis could further optimize the predictive armory of response EGFR monoclonal antibodies [104]. The NCCN treatment guidelines (version 2.2017) recommend assessment of colorectal cancers for BRAF exon 15. In the presence of such mutation, response to cetuximab/panitumumab is deemed highly unlikely. A predictive role of PIK3CA and PTEN mutation has been suggested, but not universally applied [105].

Pancreatic Cancer

Molecular Classification

It has long been known that KRAS mutations are the predominant molecular alteration in pancreatic ductal adenocarcinoma (PDAC), occurring in more than 90% of the cases.

Beyond KRAS, additional recurrent findings have been documented and, as in colorectal cancer, different classifications for pancreatic cancer based on molecular subtypes have been developed. While a number of these classifications rely on exome sequencing [106, 107], others rely on tumor transcriptome [108–110]. TCGA study has further involved non-coding RNA expression and proteomics as part of the integrated genomic profiling [111]. While these classifications share common subgroups, variations between them exist. These variations are speculated to be partly due to the variability in tumor cellularity/contamination with non-malignant cells in the tumor, differences in experimental and analytical models, as well as differences in data quality.

One classification, relying on PDAC transcriptome, proposed four subtypes of squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine (ADEX). In addition to activating mutations in KRAS (92%), mutations affecting ten distinct pathways were described, resulting in disruption of G1/S checkpoint mechanism (78%), TGF-B signaling (47%), histone modification (24%), and BRCA mutations (BRCA1, BRCA2, ATM, and PALB2; 5% germline and 12% somatic) [108]. Wadell et al. proposed a classification mechanism with reliance on structural variation events [106]. Unstable subtype (subtype 4), which accounted for 14% of samples in this study, represented features typical of pancreatic cancer tumors with BRCAness.

Furthermore (as outlined in the previous section on Colorectal Cancer), identifying patients with hereditary pancreatic cancer syndromes can drive personalized screening schemas in affected families and might offer personalized treatment options in affected individuals.

Clinical Utility of Molecular Analysis in Pancreatic Cancer

KRAS Mutations

Activating mutation of KRAS is seen in ~90% of pancreatic cancer patients. Attempts to target KRAS mutations directly have failed so far, although promising new approaches are being pursued [112]. Indirect targeting of the mutation through combination therapies with MEK and EGFR or HER3 inhibitors showed promising results in preclinical studies [113]. Clinical studies of these combinations demonstrated anti-tumor activity but were associated with extensive toxicity [114, 115]. Other common mutations in pancreatic cancer are mutations in tumor suppressor genes such as CDKN2A, TP53, SMAD, and BRCA. Some of these alterations might be amenable to synthetic lethality strategies.

BRCA1/2 Mutations/BRCAness

As previously discussed (see section on Small Bowel Adenocarcinoma), deficient DNA damage repair including deficient DDR in the context of BRCAness might make pancreatic cancer cells susceptible to platinum chemotherapy and ATM/ATR/PARP inhibitors. A phase II study of single-agent veliparib (PAPR inhibitor) as second-line treatment in patients with previously treated BRCA-mutated pancreatic adenocarcinoma (PAC) showed disappointing data with no partial response and only 25% stable disease by 4 months [116]. The role of PARP inhibition in combination with chemotherapy or as maintenance therapy is the subject of ongoing studies. Although prior studies have suggested response to platinum chemotherapy in BRCA-mutated PACs, they have shown response to other chemotherapies including gemcitabine as well. It is therefore not clear whether improved responses are platinum-specific [117].

Mismatch Repair Deficiency

Mismatch repair deficiency is only present in ~2% of all pancreatic cancers. Testing using NGS can reveal this feature that is highly predictive of response to immune check point inhibitors.

Metabolic Pathways

Mutations in metabolism pathway genes—including PI3k, HIF, MYC, and P53—are common in pancreatic cancer. CPI-613 is a potent inhibitor of alpha-ketoglutarate dehydrogenase (KGDH), one of the key glycolysis enzymes [118]. Tolerability of CPI-613 in combination with FOLFIRINOX (leucovorin, 5-FU, irinotecan, oxaliplatin) has been established [119]. Effectiveness of CPI-613 in pancreatic cancer in combination with FOLFIRINOX is under active evaluation (NCT03374852).

Nuclear Export Factor

Over-activation of nuclear export of tumor suppressor proteins has been demonstrated, in preclinical models, to inhibit function of these proteins without the need for inactivating mutation of their corresponding genes. This has been demonstrated in particular for overexpression of Exportin 1 or chromosomal region maintenance protein 1 (CRM1) [120]. Selinexor is a reversible inhibitor of CRM1, designed with the intention of nuclear retention of tumor suppressors such as APC, P53, Rb, BRCA1, and P27. Preclinical studies in pancreatic cancer showed early promise for combination of selinexor and gemcitabine [121]. A phase Ib/II trial of selinexor combined with gemcitabine/abraxane is ongoing (NCT02178436).

Hepatocellular Carcinoma

Molecular Classification

Integrated genomic analysis of 363 hepatocellular carcinoma (HCC) cases by TCGA suggested the presence of three

major HCC subtypes with prognostic implications [122]. Mutational analysis suggested IDH 1/2 mutation in a subset of samples with close similarity to what is seen in cholangiocarcinoma. Immune phenotyping of HCC revealed a subtype with high immune infiltration with potential for response to immune checkpoint inhibitors. Mutation and pathway analysis suggested a potential therapeutic role for inhibitors of WNT, MDM4 (plays a role in apoptosis regulation), MET, VEGFA, and TERT (telomerase reverse transcriptase). Methylation profiling suggested the presence of four hypermethylation clusters. Cluster 1 was significantly associated with hepatitis B virus (HBV) infection. HBV-associated tumors were more likely to be P53 mutated and less likely to be TERT mutated. Cluster 4 was significantly associated with hepatitis C virus (HCV) infection. Tumors in this cluster had high prevalence of CDKN2A (a tumor suppressor) epigenetic silencing, CTNNB1 (gene encoding beta-catenin with roles in cell-cell adhesion and protein transcription regulation) mutation, and TERT promoter mutations. Cluster 3 contained all of the samples with IDH1/2 (crucial role in cell metabolism) mutation. Different mutational landscape and methylation profiles in HBV- and HCV-infected patients therefore suggest a possibility of differential treatment based on etiology of the HCC.

Clinical Utility of Molecular Analysis in Hepatocellular Carcinoma

Possible response to immunotherapies has been suspected due to presence of immune infiltration in the tumor. This suspicion was confirmed after the CheckMate 040 trial, which established the role of nivolumab for second-line treatment of HCC (post sorafenib) [123]. The role of pembrolizumab in treatment of HCC is under evaluation (NCT02702401). Genomic studies further proposed a potential for targeting WNT, MDM4, MET, VEGFA, and TERT. Therefore, multi-target TKIs were tested for efficacy in HCC. Sorafenib, lenvatinib, and regorafenib are examples of such multi-target TKIs established as treatments in HCC. The role of specific TKIs, such as c-MET inhibitors, is under active evaluation [124]. Cabozantinib has proven survival benefit in patients with advanced HCC in the second- or third-line setting as opposed to placebo [125].

Fibroblast Growth Factor Signaling

Fibroblast growth factors (FGFs) are a family of growth factors composed on 20-plus members in humans, encoded by different genes. FGFs have the ability to bind to FGF receptors (FGFRs), leading to activation of their intracellular tyrosine kinase domain [126]. Different FGFs and FGFRs are connected to HCC tumorigenesis and metastasis [127–129]. FGF signaling is further connected to resistance to sorafenib in HCC [130]. Brivanib, a combined VEGF and FGF inhibitor, was studied in HCC post sorafenib, without significant improvement in survival when compared to placebo [131]. Among different FGF signaling pathways, FGF19/FGFR4 signaling is suspected to play a major role in resistance to sorafenib [132]. Specific FGFR4 inhibitors are studied in subsets of HCCs with high FGFR4 or FGF19 expression by IHC. A phase I study of BLU-554 (FGFR4 inhibitor) in heavily pretreated HCCs with FGF19 positivity by IHC showed good tolerability and promising responses [133]. The efficacy of a combination of FGF401 (FGFR4 inhibitor) with PDR001 (PD-1 inhibitor) in patients with FGFR4-positive HCCs is being explored in a phase II trial (NCT02325739).

Cholangiocarcinoma

Molecular Classification

Analysis of 38 liver fluke-negative intrahepatic and hepatitis-negative cholangiocarcinoma (CCA) samples by TCGA demonstrated 4 molecularly distinct subtypes that were associated with anatomical location. Among the four subtypes, CCA-harboring mutations in IDH1/2 genes was a group with aberrant mitochondrial and chromatin regulator gene expression and preferential intrahepatic location. This study also tested similarities between this subclass and the IDH 1/2 mutant HCC subtype, suggesting the possibility of similar therapeutic management. It is speculated that cholangiocarcinoma developing in the context of other risk factors, including liver flukes and hepatitis B and C infection, might have different molecular spectra. Such samples were excluded from this TCGA study [134].

In another study of 260 biliary tract cancers, distinct molecular features were seen among cancers of different anatomic locations. While intrahepatic CCA samples harbored frequent FGFR2 fusion genes and IDH1/2 mutation, extrahepatic cancers more frequently harbored PRKACA or PRKACB gene fusions. Gall bladder cancers frequently carried EGFR, ERBB3, and PTEN mutations. Common bile duct cancers were enriched for BRCA1, BRCA2, and PI3K mutations. This translated to presence of genetic alterations in nearly 40% of biliary tract cancers. A subtype of tumors harbored a high number of somatic mutations with possibility of a role for immune checkpoint inhibitors [135].

Clinical Utility of Molecular Analysis in Cholangiocarcinoma

Genomic evaluation has shown multiple mutations with potential for therapeutic targeting in cholangiocarcinoma [136].

FGFR Gene Fusions

FGFR2 gene fusions are reported in 11–45% of patients with intrahepatic CCAs [137]. The preliminary result of the phase

II study of BGJ398 (small molecule tyrosine kinase, pan FGFR inhibitor) showed promising results in CCA patients, when directed to those with FGFR fusions or FGFR gene alterations [138]. Multiple other small molecule TKIs with ability to target FGFR are targets of early-phase trials.

IDH1/2 Inhibitors

IDH1/2 mutations are common in intrahepatic CCAs, as compared to other CCAs (~25% vs. 5%) [137]. After a promising phase I study, AG-120 (oral small molecule inhibitor of IDH1) is being evaluated in a phase III study for treatment of advanced previously treated CCAs with IDH-1 mutation (NCT02989857). AG-221, an oral IDH-2 inhibitor, is also under early phase I/II study for advanced solid tumors including intrahepatic CCA with IDH-2 mutation (NCT02273739).

Immune Checkpoint Inhibitors

As part of the KEYNOTE-028 phase I study, the role of pembrolizumab in patients with advanced biliary tract cancer with detectable PD-L1 expression was evaluated. Nearly 1/3 of patients achieved disease control (partial response or stable disease).

Other Targeted Therapies

Targeting PRKACA and PRKACB fusions, EGFR/HER2(ERBB2)/ERBB3, PI3K-AKT-mTOR, RAF/MEK/ERK and hedgehog signaling is also being explored actively in different phase clinical trials [137].

Overall, malignancies of the biliary tract are rich in potentially targetable molecular lesions. In light of limited chemotherapeutic options, early molecular testing using next-generation DNA sequencing technologies should be strongly considered.

Gastroentropancreatic Neuroendocrine Tumors (GEP-NETs)

Molecular Classification

Gastrointestinal neuroendocrine tumors (NETs) are a heterogeneous group of tumors arising from the enterochromaffin cells of the gut. Pancreatic neuroendocrine tumors (PanNETs) normally arise from the islets of the Langerhans. NETs can be classified on the basis of hormone secretions as functional and non-functional, and anatomically as foregut, midgut, and hindgut tumors. But, more importantly, based on the level of differentiation and histologic grade, these tumors are classified into well-differentiated (low and intermediate grade) and poorly differentiated (high grade). The latter classification has prognostic and therapeutic value [139]. Clinical utility of the classification based on grade, however, has been challenging. Despite pathologic similarity, tumors of each category can have distinct prognostic and biologic behavior. Expanded molecular analysis of these tumors might result in improved prognostic classification and guide therapeutic interventions.

Small intestine NETs (SI-NETs) are the most common NET. The genomic landscape of SI-NETs has been evaluated in two separate studies. Banck et al. showed that SI-NETs overall harbor a low somatic mutation load [140]. Observed somatic gene mutations were mostly non-recurrent. However, these mutations had the tendency to cluster into distinct molecular pathways. In about 46% of the studies, SI-NETs had mutated or deleted SMAD genes, 23% had amplified SRC gene, and 29% had genetic alterations in the PI3K/Akt/mTOR pathways. AURKA amplification (19%) and alterations in PDFGR (20%) were also common. Overall, 72% of the patients in this study had genetic alterations that were potentially actionable [140]. Francis et al. confirmed the paucity of recurrent somatic gene alterations in SI-NETs. CDKN1B was the most frequent somatic recurrent gene alteration found in this study (10%). Chromosomal arm level copy number gains or losses were frequent findings in these tumors [141].

PanNETs are the second most common NET after SI-NETs. Scaroa et al. showed presence of germline mutations in MUTYH, CHEK2, BRCA2, MEN1, and VHL in 17% of clinically sporadic pancreatic NETs. Somatic gene mutations and deletions were clustered in four main pathways: chromatin remodeling, mTOR signaling, DNA damage repair, and telomerase maintenance [142]. Somatic mutations of MEN1 (35%), activated mTOR signaling (14%), and DAXX (apoptotic regulator) or ARTX (chromatin modified) (40%) are among the most frequent somatic mutations in PanNETs [143–145]. Less than 10% of PanNETs happen as part of familial cancer syndromes. Mutations of VHL, MEN1, TSC1, TSC2, and neurofibromatosis type 1 (NF1) genes account for the majority of these cases [146–148]. It is noteworthy that poorly differentiated PanNETs are a distinct category of PanNETs with completely different biology and gene expression and were not the focus of the aforementioned studies. Poorly differentiated neuroendocrine tumors have a high mutational burden. The most common mutations in this group consist of TP53 (53%), KRAS (30%), PI3K/PTEN (22%), and BRAF (13%) mutations [149].

As shown above, recurrent somatic genetic mutations are rare in SI-NETs. MEN1, DAXX, and ARTX—three of the most common mutated genes in PanNETs—have well-developed roles in chromatin remodeling and epigenetic regulation. Dysregulated epigenetic mechanism therefore has been the focus of interest as a potential regulator of gastroentropancreatic NETs (GEP-NETs). DNA methylation, histone modification, and posttranscriptional modification by non-encoding RNAs are three of the epigenetic regulator mechanisms. How-Kit et al. used DNA methylation profile as a tool to distinguish different subtypes of GEP-NETs [150].

They found a different methylation profile for each of the PanNETs and proposed two distinct methylation profiles for SI-NETs. The role of DNA methylation patterns and histone modifications, as well as expression patterns of non-encoding RNAs as prognostic factors or predictors of metastasis pattern, has been investigated, but has not gained meaningful clinical application yet [151–153].

Clinical Utility of Molecular Analysis in GEP-NETs

The mTOR pathway is a crucial regulator of cell proliferation, apoptosis, angiogenesis, and metabolism [154]. Activating mutations of mTOR pathway genes are a common finding in both PanNETs (14%) and SI-NETs (29%) as described previously. Expression profiling of PanNETs has showed downregulation of tuberous sclerosis-2 (TSC-2) and phosphatase and tensin homolog (PTEN)—two of the inhibitory regulators of mTOR pathway in 2/3 of studied tumors [145]. Inactivating mutations of MEN1 are frequently observed in both hereditary and non-hereditary forms of PanNETs. These mutations result in removal of key inhibitors of the mTOR pathway, therefore constitutively activating the pathway [155]. Inhibition of mTOR pathway has therefore been a therapeutic approach of interest in NETs. Everolimus (an mTOR inhibitor) has gained FDA approval for treatment of progressive well-differentiated non-functional NETs of the pancreas and lung based on a phase III study (RADIANT-4) [156]. The role of everolimus for grade 3 tumors is under ongoing investigation (NCT02113800, NCT02687958, NCT02695459, NCT02248012). Sapanisertib, a small molecule mTOR inhibitor, is the subject of a phase II study for refractory G1-2 PanNETs.

Epigenetic mechanism dysregulation, as mentioned previously, is an area of active investigation in NETs. Histone deacetylase (HDAC) is a regulator enzyme crucial for chromatin remodeling. Preclinical studies suggested a role of HDAC inhibitors in inhibiting NET cell growth. HDAC inhibitor panobinostat has been studied in phase II clinical trial for control of metastatic low-grade NETs and showed low response rate, but high stable disease [157]. Belinostat (another HDAC inhibitor) in combination with cisplatin and etoposide has been studied in a phase I trial for grade 3 NETs, the results of which are not published yet (NCT00926640). A therapeutic role of targeting DNA methylation in NETs is not well established yet.

Challenges and Future Perspectives

Genomic Complexity, Prioritization, and Co-occurring Mutations

Comprehensive analysis of cancer genomes has revealed diverse genetic abnormalities even within cancers of a single type. An individual tumor frequently carries multiple mutations, not all carrying the same weight in driving cancer. Among individuals with the same cancer type, some mutations that are likely driving cancer progression are therapeutically targetable but occur with low frequency. Therefore, establishment of the role of such mutations in a given tumor type through conventional trials is challenging. Novel clinical trial approaches—such as basket and umbrella trials as well as systematic links between molecular profiling laboratories and institutions conducting clinical trials—will be crucial for overcoming this limitation. It has become clear that coexisting mutations might regulate sensitivity to targeted therapies [158].

It is now common practice to obtain NGS results for GI cancers, which frequently reveals more than one targetable mutation. Assuming targeted therapy for all actionable mutations is available, prioritizing the choice of treatment becomes a challenge. While access to an institutional molecular tumor board might help in such situations, use of preclinical animal models and/or computational platforms might be increasingly relevant help [159, 160].

Dynamic Changes

Even though during drug development molecular pathways are mostly considered as linear, what exists in real life is a complex network of pathways. Blockade of one single pathway can therefore lead to a shift to other pathways or be bypassed by arbitrary pathways, hence resulting in a lack of efficacy of such a drug or development of resistance [161]. With advancement in high throughput next-generation sequencing, simultaneous evaluation of multiple "omics" is available now. However, our knowledge of how to interpret all the available information is still limited. Advancements in system biology to study complex biological systems are therefore needed for such interpretations [162, 163].

Future Perspective: Treatment Monitoring Using Circulating Tumor DNA (ctDNA)

Tumor tissue biopsy remains the gold standard for diagnosis and evaluation of tumor characteristics, including tumor genomic alterations. "Liquid biopsy" is being studied increasingly as a possible alternative/adjunct to the conventional tumor biopsy. Liquid biopsy involves study of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), circulating exomes, miRNA, mRNA, and so forth. Being noninvasive, cheap, and easy to perform, this mode of biopsy is theoretically ideal for monitoring tumor characteristics over time. A recent study has established the value of large-scale ctDNA profiling by NGS in establishment of a genomic

landscape of colorectal cancer. ctDNA profiling in this study resulted in comparable frequency of genomic alterations as opposed to direct tissue sample profiling. Furthermore, this study identified new mutations in EGFR extracellular domain, which predicted resistance to EGFR antibody treatment [164]. Prior studies have shown the value of ctDNA profiling in evaluation/prediction of resistance emergence to EGFR inhibition by monitoring KRAS, NRAS, and BRAF genes [165, 166]. Further prospective trials would be needed to establish the clinical utility of liquid biopsy in colorectal cancer treatment monitoring.

Tumor Heterogeneity

The concept of spatial and temporal tumor cell heterogeneity has long been known [167, 168]. Clinically relevant questions remain:

- At the molecular level, to what extent is the biopsied section of tumor representative of the whole tumor? [169, 170].
- Are molecular characteristics of the original tumors and metastases the same?
- How are the molecular characteristics of the tumor changing over time?
- How would tumor heterogeneity affect clonal evolution and acquisition of resistance to treatment?

These are concepts that cannot be easily addressed through traditional surgical/needle biopsy. Analysis of ctDNA might help in addressing these questions since tumor DNA in the bloodstream might represent clinically relevant clones [171, 172].

Access to Tissue

To perform somatic mutation analysis of solid tumors, adequate high-quality samples are required. Typically, these are obtained either intraoperatively or through image-guided fine needle biopsy. The latter frequently provides only small amounts of cells, in particular in pancreatic cancer. Furthermore, as the potential role of genomic studies in monitoring of clonal changes occurring in tumors over time continues to expand, serial invasive biopsies are of limited utility. Evaluation of circulating tumor cells (CTC) and cell-free tumor DNA (ctDNA) can provide meaningful insights [164, 173, 174]. However, differences have been observed between results of ctDNA and tissue-based NGS DNA analysis [175]. In addition, mutations resulting from clonal hematopoiesis, but not from cancer cells, are frequently detected by ctDNA analysis and might lead to false-positive results [176]. Thus, the exact role of ctDNA in the management of gastrointestinal cancers remains to be defined.

Clinical Utility Challenges

NGS can detect potentially actionable mutations in cancer cells. Clinical availability of targeted therapies remains a practical clinical challenge—since results frequently suggest use of a particular drug outside of their approved indication. Access to drugs in such a situation is limited to clinical trials or off-label use of the targeted therapy. However, the rarity of driver/actionable mutations prevents testing of many mutation/drug pairings in clinical trials. An approach of approval of NGS tests with ongoing evidence generation, as recently proposed by the FDA, might accelerate this process [177].

Conclusion

Advances in cancer genomics have deepened our knowledge of cancer biology at a rapid and accelerating pace and have raised hopes for the development of increasingly efficacious tailored treatments for GI cancers. Further advances in high throughput technologies, tissue acquisition, and systems biology will set the stage for improved cancer diagnosis and treatment. Results of biomarker-based basket trials such as FOCUS, TAPUR, and NCI-MATCH will inform the future of precision oncology for GI malignancies and beyond.

References

1. Metzker ML. Sequencing technologies – the next generation. Nat Rev Genet. 2010;11(1):31–46.
2. Jones S, Anagnostou V, Lytle K, Parpart-Li S, Nesselbush M, Riley DR, et al. Personalized genomic analyses for cancer mutation discovery and interpretation. Sci Transl Med. 2015;7(283):283ra53.
3. Rhee JK, Lee S, Park WY, Kim YH, Kim TM. Allelic imbalance of somatic mutations in cancer genomes and transcriptomes. Sci Rep. 2017;7(1):1653.
4. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol. 1999;30(10):1213–20.
5. Blanke CD, Eisenberg BL, Heinrich MC. Gastrointestinal stromal tumors. Curr Treat Options in Oncol. 2001;2(6):485–91.
6. Du CY, Shi YQ, Zhou Y, Fu H, Zhao G. The analysis of status and clinical implication of KIT and PDGFRA mutations in gastrointestinal stromal tumor (GIST). J Surg Oncol. 2008;98(3):175–8.
7. Kolibaba KS, Druker BJ. Protein tyrosine kinases and cancer. Biochim Biophys Acta. 1997;1333(3):F217–48.
8. Savage DG, Antman KH. Imatinib mesylate–a new oral targeted therapy. N Engl J Med. 2002;346(9):683–93.
9. Nishida T, Blay JY, Hirota S, Kitagawa Y, Kang YK. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer. 2016;19(1):3–14.
10. Debiec-Rychter M, Dumez H, Judson I, Wasag B, Verweij J, Brown M, et al. Use of c-KIT/PDGFRA mutational analysis to

predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2004;40(5):689–95.
11. Nakagawara A. Trk receptor tyrosine kinases: a bridge between cancer and neural development. Cancer Lett. 2001;169(2):107–14.
12. Creancier L, Vandenberghe I, Gomes B, Dejean C, Blanchet JC, Meilleroux J, et al. Chromosomal rearrangements involving the NTRK1 gene in colorectal carcinoma. Cancer Lett. 2015;365(1):107–11.
13. Lee SJ, Li GG, Kim ST, Hong ME, Jang J, Yoon N, et al. NTRK1 rearrangement in colorectal cancer patients: evidence for actionable target using patient-derived tumor cell line. Oncotarget. 2015;6(36):39028–35.
14. Ardini E, Bosotti R, Borgia AL, De Ponti C, Somaschini A, Cammarota R, et al. The TPM3-NTRK1 rearrangement is a recurring event in colorectal carcinoma and is associated with tumor sensitivity to TRKA kinase inhibition. Mol Oncol. 2014;8(8):1495–507.
15. Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. Oncologist. 2014;19(3):235–42.
16. Potts SJ, Dean EJ, Polikoff J, Pacey S, Chiorean EG, Chee CE. Detecting NTRK, ROS1, and ALK gene fusions in gastrointestinal tumor patients. J Clin Oncol. 2017;35(4_suppl):619–619.
17. Drilon A, Siena S, Ou SI, Patel M, Ahn MJ, Lee J, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). Cancer Discov. 2017;7(4):400–9.
18. Hyman DM, Laetsch TW, Kummar S, DuBois SG, Farago AF, Pappo AS, et al. The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers. J Clin Oncol. 2017;35(suppl):abstr LBA2501.
19. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378(8):731–9.
20. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of lynch syndrome: 1895–2015. Nat Rev Cancer. 2015;15(3):181–94.
21. Liu D, Keijzers G, Rasmussen LJ. DNA mismatch repair and its many roles in eukaryotic cells. Mutat Res. 2017;773:174–87.
22. Thompson BA, Spurdle AB, Plazzer JP, Greenblatt MS, Akagi K, Al-Mulla F, et al. Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants in the InSiGHT locus-specific database. Nat Genet. 2014;46(2):107–15.
23. Weissenbach J, Gyapay G, Dib C, Vignal A, Morissette J, Millasseau P, et al. A second-generation linkage map of the human genome. Nature. 1992;359(6398):794–801.
24. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. Nat Rev Genet. 2002;3(6):415–28.
25. Herman JG, Umar A, Polyak K, Graff JR, Ahuja N, Issa JP, et al. Incidence and functional consequences of hMLH1 promoter hypermethylation in colorectal carcinoma. Proc Natl Acad Sci U S A. 1998;95(12):6870–5.
26. Valeri N, Gasparini P, Fabbri M, Braconi C, Veronese A, Lovat F, et al. Modulation of mismatch repair and genomic stability by miR-155. Proc Natl Acad Sci U S A. 2010;107(15):6982–7.
27. Yarchoan M, Johnson BA 3rd, Lutz ER, Laheru DA, Jaffee EM. Targeting neoantigens to augment antitumour immunity. Nat Rev Cancer. 2017;17(4):209–22.
28. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409–13.
29. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–20.
30. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017;18(9):1182–91.
31. Hoang LN, Gilks BC. Hereditary breast and ovarian cancer syndrome: moving beyond BRCA1 and BRCA2. Adv Anat Pathol. 2018;25:85–95.
32. Abkevich V, Timms KM, Hennessy BT, Potter J, Carey MS, Meyer LA, et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. Br J Cancer. 2012;107(10):1776–82.
33. Timms KM, Abkevich V, Hughes E, Neff C, Reid J, Morris B, et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. Breast Cancer Res. 2014;16(6):475.
34. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer. 2004;4(10):814–9.
35. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917–21.
36. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434(7035):913–7.
37. Maxwell KN, Wubbenhorst B, Wenz BM, De Sloover D, Pluta J, Emery L, et al. BRCA locus-specific loss of heterozygosity in germline BRCA1 and BRCA2 carriers. Nat Commun. 2017;8(1):319.
38. Walsh CS, Ogawa S, Scoles DR, Miller CW, Kawamata N, Narod SA, et al. Genome-wide loss of heterozygosity and uniparental disomy in BRCA1/2-associated ovarian carcinomas. Clin Cancer Res. 2008;14(23):7645–51.
39. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244–50.
40. Weber AM, Ryan AJ. ATM and ATR as therapeutic targets in cancer. Pharmacol Ther. 2015;149:124–38.
41. Kaplan R. The FOCUS4 design for biomarker stratified trials. Chin Clin Oncol. 2015;4(3):35.
42. Basourakos SP, Li L, Aparicio AM, Corn PG, Kim J, Thompson TC. Combination platinum-based and DNA damage response-targeting cancer therapy: evolution and future directions. Curr Med Chem. 2017;24(15):1586–606.
43. Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet. 2012;379(9824):1428–35.
44. Hainsworth JD, Rubin MS, Spigel DR, Boccia RV, Raby S, Quinn R, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon research institute. J Clin Oncol. 2013;31(2):217–23.
45. Kato S, Krishnamurthy N, Banks KC, De P, Williams K, Williams C, et al. Utility of genomic analysis in circulating tumor DNA from patients with carcinoma of unknown primary. Cancer Res. 2017;77(16):4238–46.
46. Whitcomb DC, Shelton CA, Brand RE. Genetics and genetic testing in pancreatic cancer. Gastroenterology. 2015;149(5):1252–64. e4.
47. Grant RC, Selander I, Connor AA, Selvarajah S, Borgida A, Briollais L, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015;148(3):556–64.

48. Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer. 2008;113(7 Suppl):1807–43.
49. Petrovchich I, Ford JM. Genetic predisposition to gastric cancer. Semin Oncol. 2016;43(5):554–9.
50. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167–75.
51. Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res. 2013;19(2):462–8.
52. Cancer Genome Atlas Research N, Analysis Working Group: Asan U, Agency BCC, Brigham, Women's H, Broad I, et al. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017;541(7636):169–75.
53. Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–9.
54. Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015;21(5):449–56.
55. Janjigian YY, Bendell J, Calvo E, Kim JW, Ascierto PA, Sharma P. CheckMate-032: phase I/II, open-label study of safety and activity of nivolumab (nivo) alone or with ipilimumab (ipi) in advanced and metastatic (A/M) gastric cancer (GC). ASCO meeting abstracts. Abstract 4010.
56. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol. 2016;17(6):717–26.
57. Rima FA, Hussain M, Haque N, Dewan RK, Rahman N, Jinnah MA, et al. HER2 status in gastric and gastroesophageal junction adenocarcinoma. Mymensingh Med J. 2017;26(2):372–9.
58. Kunz PL, Mojtahed A, Fisher GA, Ford JM, Chang DT, Balise RR, et al. HER2 expression in gastric and gastroesophageal junction adenocarcinoma in a US population: clinicopathologic analysis with proposed approach to HER2 assessment. Appl Immunohistochem Mol Morphol. 2012;20(1):13–24.
59. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
60. Kang YK, Rha SY, Tassone P, Barriuso J, Yu R, Szado T, et al. A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer. Br J Cancer. 2014;111(4):660–6.
61. Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, Song C, et al. Pertuzumab (P) + trastuzumab (H) + chemotherapy (CT) for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (mGC/GEJC): final analysis of a phase III study (JACOB). European Society for Medical Oncology (ESMO) 2017 Congress; September 8–12, 2017; Madrid, Spain; 2017.
62. Hyman DM, Piha-Paul S, Rodon J. Neratinib in HER2- or HER3-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 'basket' study. AACR annual meeting; Washington, DC; 2017.
63. Oh SY, Kwon HC, Kim SH, Jang JS, Kim MC, Kim KH, et al. Clinicopathologic significance of HIF-1alpha, p53, and VEGF expression and preoperative serum VEGF level in gastric cancer. BMC Cancer. 2008;8(1):123.
64. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9.
65. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224–35.
66. Fuchs CS, Shitara K, Di Bartolomeo M, Lonardi S, Al-Batran SE, Custem EV, et al. RAINFALL: a randomized, double-blind, placebo-controlled phase III study of cisplatin (Cis) plus capecitabine (Cape) or 5FU with or without ramucirumab (RAM) as first-line therapy in patients with metastatic gastric or gastroesophageal junction (G-GEJ) adenocarcinoma. J Clin Oncol. 2018;36(suppl 4S):abstr 5; Chicago 2018.
67. Peng DF, Sugihara H, Mukaisho K, Tsubosa Y, Hattori T. Alterations of chromosomal copy number during progression of diffuse-type gastric carcinomas: metaphase- and array-based comparative genomic hybridization analyses of multiple samples from individual tumours. J Pathol. 2003;201(3):439–50.
68. Bang YJ, Van Cutsem E, Mansoor W, Petty RD, Chao Y, Cunningham D, Ferry DR, Smith NR, Frewer P, Ratnayake J, Stockman PK, Kilgour E, Landers D. A randomized, open-label phase II study of AZD4547 (AZD) versus Paclitaxel (P) in previously treated patients with advanced gastric cancer (AGC) with Fibroblast Growth Factor Receptor 2 (FGFR2) polysomy or gene amplification (amp): SHINE study. J Clin Oncol. 2015;33(Suppl):abstr 4014.
69. Catenacci DVT, Rha SU, Bang YJ, Wainberg ZA, Chao J, Lee KW. Updated antitumor activity and safety of FPA144, an ADCC-enhanced, FGFR2b isoform-specific monoclonal antibody, in patients with FGFR2b+ gastric cancer. J Clin Oncol. 2017;35(15_suppl):4067; Chicago 2017.
70. Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol. 2013;31(31):3935–43.
71. Lim SM, Park HS, Kim S, Kim S, Ali SM, Greenbowe JR, et al. Next-generation sequencing reveals somatic mutations that confer exceptional response to everolimus. Oncotarget. 2016;7(9):10547–56.
72. Overman MJ, Hu CY, Kopetz S, Abbruzzese JL, Wolff RA, Chang GJ. A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. Ann Surg Oncol. 2012;19(5):1439–45.
73. Schrock AB, Devoe CE, McWilliams R, Sun J, Aparicio T, Stephens PJ, et al. Genomic profiling of small-bowel adenocarcinoma. JAMA Oncol. 2017;3(11):1546–53.
74. Cancer Genome Atlas N. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330–7.
75. Rodriguez-Salas N, Dominguez G, Barderas R, Mendiola M, Garcia-Albeniz X, Maurel J, et al. Clinical relevance of colorectal cancer molecular subtypes. Crit Rev Oncol Hematol. 2017;109:9–19.
76. Guinney J, Dienstmann R, Wang X, de Reynies A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015;21(11):1350–6.
77. Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic

colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol. 2017;3:194–201.
78. Venook A, Niedzwiecki D, Innocenti F, Fruth B, Greene C, O'Neil BH. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol. 2016;34(15_suppl):3504–3504.
79. Yaeger R, Chatila WK, Lipsyc MD, Hechtman JF, Cercek A, Sanchez-Vega F, et al. Clinical sequencing defines the genomic landscape of metastatic colorectal cancer. Cancer Cell. 2018;33(1):125–36.e3.
80. Weisenberger DJ, Siegmund KD, Campan M, Young J, Long TI, Faasse MA, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. Nat Genet. 2006;38(7):787–93.
81. Sadanandam A, Wang X, de Sousa EMF, Gray JW, Vermeulen L, Hanahan D, et al. Reconciliation of classification systems defining molecular subtypes of colorectal cancer: interrelationships and clinical implications. Cell Cycle. 2014;13(3):353–7.
82. Anastas JN, Moon RT. WNT signalling pathways as therapeutic targets in cancer. Nat Rev Cancer. 2013;13(1):11–26.
83. Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. Oncogene. 2017;36(11):1461–73.
84. Polakis P. Wnt signaling in cancer. Cold Spring Harb Perspect Biol. 2012;4(5):a008052.
85. Krishnamurthy N, Kurzrock R. Targeting the Wnt/beta-catenin pathway in cancer: update on effectors and inhibitors. Cancer Treat Rev. 2017;13(62):50–60.
86. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature. 2012;483(7387):100–3.
87. Kopetz S, McDonough SL, Morris VK, Lenz HJ, Magliocco AM, Atreya CE. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG 1406). J Clin Oncol. 2017;35(4_suppl):520.
88. Tang Z, Yuan X, Du R, Cheung SH, Zhang G, Wei J, et al. BGB-283, a novel RAF kinase and EGFR inhibitor, displays potent antitumor activity in BRAF-mutated colorectal cancers. Mol Cancer Ther. 2015;14(10):2187–97.
89. Atreya CE, Van Custem E, Bendell JC, et al. Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E mutated (BRAFm) metastatic colorectal cancer (mCRC). J Clin Oncol. 2015;33(15_suppl):103.
90. Van Cutsem E, Cuyle P-J, Huijberts S, et al. BEACON CRC study safety lead-in (SLI) in patients with BRAF V600E metastatic colorectal cancer: efficacy and tumor markers. J Clin Oncol. 2018;36(4_suppl):627.
91. Kopetz S, Grothey A, Yaeger R, et al. Updated results of the BEACON CRC safety lead-in: Encorafenib (ENCO) + binimetinib (BINI) + cetuximab (CETUX) for BRAFV600E-mutated metastatic colorectal cancer (mCRC). J Clin Oncol. 2019;37(4_suppl):688.
92. National Comprehensive Cancer Network. Colon Cancer (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed 11 May 2019.
93. Siena S, Sartore-Bianchi A, Trusolino L, et al. Final results of the HERACLES trial in HER2-amplified colorectal cancer. 2017 AACR annual meeting; presented April 2, 2017.
94. Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28(20):3219–26.
95. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med. 2003;349(3):247–57.
96. Klingbiel D, Saridaki Z, Roth AD, Bosman FT, Delorenzi M, Tejpar S. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. Ann Oncol. 2015;26(1):126–32.
97. Sinicrope FA, Mahoney MR, Smyrk TC, Thibodeau SN, Warren RS, Bertagnolli MM, et al. Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy. J Clin Oncol. 2013;31(29):3664–72.
98. Hutchins G, Southward K, Handley K, Magill L, Beaumont C, Stahlschmidt J, et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. J Clin Oncol. 2011;29(10):1261–70.
99. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol. 2005;23(3):609–18.
100. Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. J Clin Oncol. 2009;27(24):3975–80.
101. Lievre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res. 2006;66(8):3992–5.
102. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013;369(11):1023–34.
103. Pietrantonio F, Petrelli F, Coinu A, Di Bartolomeo M, Borgonovo K, Maggi C, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J Cancer. 2015;51(5):587–94.
104. Yamazaki K, Yoshino T, Tsuchihara K, Shinozaki E, Muro K, Nishina T, et al. Clinical impact of expanded BRAF mutational status on the outcome for metastatic colorectal cancer patients with anti-EGFR antibody: an analysis of the BREAC trial (Biomarker Research for Anti-EGFR Monoclonal Antibodies by Comprehensive Cancer Genomics). J Clin Oncol. 2015;33:abstract # 573.
105. Therkildsen C, Bergmann TK, Henrichsen-Schnack T, Ladelund S, Nilbert M. The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: a systematic review and meta-analysis. Acta Oncol. 2014;53(7):852–64.
106. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
107. Witkiewicz AK, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, et al. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. Nat Commun. 2015;6:6744.
108. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531(7592):47–52.
109. Collisson EA, Sadanandam A, Olson P, Gibb WJ, Truitt M, Gu S, et al. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. Nat Med. 2011;17(4):500–3.
110. Moffitt RA, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015;47(10):1168–78.
111. Cancer Genome Atlas Research Network. Electronic address aadhe, cancer genome atlas research N. Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell. 2017;32(2):185–203.e13.
112. Yuan TL, Fellmann C, Lee CS, Ritchie CD, Thapar V, Lee LC, et al. Development of siRNA payloads to target KRAS-mutant cancer. Cancer Discov. 2014;4(10):1182–97.

113. Mirzoeva OK, Collisson EA, Schaefer PM, Hann B, Hom YK, Ko AH, et al. Subtype-specific MEK-PI3 kinase feedback as a therapeutic target in pancreatic adenocarcinoma. Mol Cancer Ther. 2013;12(10):2213–25.
114. Ko AH, Bekaii-Saab T, Van Ziffle J, Mirzoeva OM, Joseph NM, Talasaz A, et al. A multicenter, open-label phase II clinical trial of combined MEK plus EGFR inhibition for chemotherapy-refractory advanced pancreatic adenocarcinoma. Clin Cancer Res. 2016;22(1):61–8.
115. Lieu CH, Hidalgo M, Berlin JD, Ko AH, Cervantes A, LoRusso P, et al. A phase Ib dose-escalation study of the safety, tolerability, and pharmacokinetics of cobimetinib and duligotuzumab in patients with previously treated locally advanced or metastatic cancers with mutant KRAS. Oncologist. 2017;22(9):1024–e89.
116. Lowery MA, Kelsen DP, Capanu M, Smith SC, Lee JW, Stadler ZK, et al. Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma. Eur J Cancer. 2018;89:19–26.
117. Lohse I, Borgida A, Cao P, Cheung M, Pintilie M, Bianco T, et al. BRCA1 and BRCA2 mutations sensitize to chemotherapy in patient-derived pancreatic cancer xenografts. Br J Cancer. 2015;113(3):425–32.
118. Stuart SD, Schauble A, Gupta S, Kennedy AD, Keppler BR, Bingham PM, et al. A strategically designed small molecule attacks alpha-ketoglutarate dehydrogenase in tumor cells through a redox process. Cancer Metab. 2014;2(1):4.
119. Alistar A, Morris BB, Desnoyer R, Klepin HD, Hosseinzadeh K, Clark C, et al. Safety and tolerability of the first-in-class agent CPI-613 in combination with modified FOLFIRINOX in patients with metastatic pancreatic cancer: a single-centre, open-label, dose-escalation, phase 1 trial. Lancet Oncol. 2017;18(6):770–8.
120. Turner JG, Dawson J, Sullivan DM. Nuclear export of proteins and drug resistance in cancer. Biochem Pharmacol. 2012;83(8):1021–32.
121. Kazim S, Malafa MP, Coppola D, Husain K, Zibadi S, Kashyap T, et al. Selective nuclear export inhibitor KPT-330 enhances the antitumor activity of gemcitabine in human pancreatic cancer. Mol Cancer Ther. 2015;14(7):1570–81.
122. Cancer Genome Atlas Research Network. Electronic Address Wbe, Cancer Genome Atlas Research Network. Comprehensive and integrative genomic characterization of hepatocellular carcinoma. Cell. 2017;169(7):1327–41.e23.
123. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492–502.
124. de Rosamel L, Blanc JF. Emerging tyrosine kinase inhibitors for the treatment of hepatocellular carcinoma. Expert Opin Emerg Drugs. 2017;22(2):175–90.
125. Abou-Alfa GK, Meyer T, Cheng A-L. Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: results from the randomized phase III CELESTIAL trial. J Clin Oncol. 2018;36(suppl 4S):abstr 208.
126. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer. 2010;10(2):116–29.
127. Gauglhofer C, Sagmeister S, Schrottmaier W, Fischer C, Rodgarkia-Dara C, Mohr T, et al. Up-regulation of the fibroblast growth factor 8 subfamily in human hepatocellular carcinoma for cell survival and neoangiogenesis. Hepatology. 2011;53(3):854–64.
128. Uriarte I, Latasa MU, Carotti S, Fernandez-Barrena MG, Garcia-Irigoyen O, Elizalde M, et al. Ileal FGF15 contributes to fibrosis-associated hepatocellular carcinoma development. Int J Cancer. 2015;136(10):2469–75.
129. Zhao H, Lv F, Liang G, Huang X, Wu G, Zhang W, et al. FGF19 promotes epithelial-mesenchymal transition in hepatocellular carcinoma cells by modulating the GSK3beta/beta- catenin signaling cascade via FGFR4 activation. Oncotarget. 2016;7(12):13575–86.
130. Tovar V, Cornella H, Moeini A, Vidal S, Hoshida Y, Sia D, et al. Tumour initiating cells and IGF/FGF signalling contribute to sorafenib resistance in hepatocellular carcinoma. Gut. 2017;66(3):530–40.
131. Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol. 2013;31(28):3509–16.
132. Gao L, Wang X, Tang Y, Huang S, Hu CA, Teng Y. FGF19/FGFR4 signaling contributes to the resistance of hepatocellular carcinoma to sorafenib. J Exp Clin Cancer Res. 2017;36(1):8.
133. Kang Y-K, Macarulla T, Yau T. Clinical activity of Blu-554, a potent, highly-selective FGFR4 inhibitor in advanced hepatocellular carcinoma (HCC) with FGFR4 pathway activation. ILCA annual conference; Seoul, South Korea 2017.
134. Farshidfar F, Zheng S, Gingras MC, Newton Y, Shih J, Robertson AG, et al. Integrative genomic analysis of cholangiocarcinoma identifies distinct IDH-mutant molecular profiles. Cell Rep. 2017;18(11):2780–94.
135. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, et al. Genomic spectra of biliary tract cancer. Nat Genet. 2015;47(9):1003–10.
136. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma – evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2017;15:95–111.
137. Rizvi S, Gores GJ. Emerging molecular therapeutic targets for cholangiocarcinoma. J Hepatol. 2017;67(3):632–44.
138. Javle MM, Shroff RT, Zhu A, Sadeghi S, Choo S, et al. A phase 2 study of BGJ398 in patients (pts) with advanced or metastatic FGFR-altered cholangiocarcinoma (CCA) who failed or are intolerant to platinum-based chemotherapy. J Clin Oncol. 2016;34(4_suppl):335.
139. Cives M, Strosberg J. An update on gastroenteropancreatic neuroendocrine tumors. Oncology (Williston Park). 2014;28(9):749–56, 58.
140. Banck MS, Kanwar R, Kulkarni AA, Boora GK, Metge F, Kipp BR, et al. The genomic landscape of small intestine neuroendocrine tumors. J Clin Invest. 2013;123(6):2502–8.
141. Francis JM, Kiezun A, Ramos AH, Serra S, Pedamallu CS, Qian ZR, et al. Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. Nat Genet. 2013;45(12):1483–6.
142. Scarpa A, Chang DK, Nones K, Corbo V, Patch AM, Bailey P, et al. Whole-genome landscape of pancreatic neuroendocrine tumours. Nature. 2017;543(7643):65–71.
143. Corbo V, Dalai I, Scardoni M, Barbi S, Beghelli S, Bersani S, et al. MEN1 in pancreatic endocrine tumors: analysis of gene and protein status in 169 sporadic neoplasms reveals alterations in the vast majority of cases. Endocr Relat Cancer. 2010;17(3):771–83.
144. Jiao Y, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science. 2011;331(6021):1199–203.
145. Missiaglia E, Dalai I, Barbi S, Beghelli S, Falconi M, della Peruta M, et al. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. J Clin Oncol. 2010;28(2):245–55.
146. Lubensky IA, Pack S, Ault D, Vortmeyer AO, Libutti SK, Choyke PL, et al. Multiple neuroendocrine tumors of the pancreas in von Hippel-Lindau disease patients: histopathological and molecular genetic analysis. Am J Pathol. 1998;153(1):223–31.

147. Starker LF, Carling T. Molecular genetics of gastroenteropancreatic neuroendocrine tumors. Curr Opin Oncol. 2009;21(1):29–33.
148. Larson AM, Hedgire SS, Deshpande V, Stemmer-Rachamimov AO, Harisinghani MG, Ferrone CR, et al. Pancreatic neuroendocrine tumors in patients with tuberous sclerosis complex. Clin Genet. 2012;82(6):558–63.
149. Vijayvergia N, Boland PM, Handorf E, Gustafson KS, Gong Y, Cooper HS, et al. Molecular profiling of neuroendocrine malignancies to identify prognostic and therapeutic markers: a fox chase cancer center pilot study. Br J Cancer. 2016;115(5):564–70.
150. How-Kit A, Dejeux E, Dousset B, Renault V, Baudry M, Terris B, et al. DNA methylation profiles distinguish different subtypes of gastroenteropancreatic neuroendocrine tumors. Epigenomics. 2015;7(8):1245–58.
151. House MG, Herman JG, Guo MZ, Hooker CM, Schulick RD, Lillemoe KD, et al. Aberrant hypermethylation of tumor suppressor genes in pancreatic endocrine neoplasms. Ann Surg. 2003;238(3):423–31; discussion 31–2.
152. Chan AO, Kim SG, Bedeir A, Issa JP, Hamilton SR, Rashid A. CpG island methylation in carcinoid and pancreatic endocrine tumors. Oncogene. 2003;22(6):924–34.
153. Liu L, Broaddus RR, Yao JC, Xie S, White JA, Wu TT, et al. Epigenetic alterations in neuroendocrine tumors: methylation of RAS-association domain family 1, isoform a and p16 genes are associated with metastasis. Mod Pathol. 2005;18(12):1632–40.
154. Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. Nat Rev Drug Discov. 2006;5(8):671–88.
155. Wang Y, Ozawa A, Zaman S, Prasad NB, Chandrasekharappa SC, Agarwal SK, et al. The tumor suppressor protein menin inhibits AKT activation by regulating its cellular localization. Cancer Res. 2011;71(2):371–82.
156. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387(10022):968–77.
157. Jin N, Lubner SJ, Mulkerin DL, Rajguru S, Carmichael L, Chen H, et al. A phase II trial of a histone deacetylase inhibitor panobinostat in patients with low-grade neuroendocrine tumors. Oncologist. 2016;21(7):785–6.
158. Bertotti A, Papp E, Jones S, Adleff V, Anagnostou V, Lupo B, et al. The genomic landscape of response to EGFR blockade in colorectal cancer. Nature. 2015;526(7572):263–7.
159. van der Velden DL, van Herpen CML, van Laarhoven HWM, Smit EF, Groen HJM, Willems SM, et al. Molecular tumor boards: current practice and future needs. Ann Oncol. 2017;28(12):3070–5.
160. Dalton WB, Forde PM, Kang H, Connolly RM, Stearns V, Gocke CD, et al. Personalized medicine in the oncology clinic: implementation and outcomes of the Johns Hopkins molecular tumor board. JCO Precis Oncol. 2017;(1):1–19.
161. Mirzoeva OK, Das D, Heiser LM, Bhattacharya S, Siwak D, Gendelman R, et al. Basal subtype and MAPK/ERK kinase (MEK)-phosphoinositide 3-kinase feedback signaling determine susceptibility of breast cancer cells to MEK inhibition. Cancer Res. 2009;69(2):565–72.
162. Yang MQ, Yoshigoe K, Yang W, Tong W, Qin X, Dunker A, et al. The emerging genomics and systems biology research lead to systems genomics studies. BMC Genomics. 2014;15(Suppl 11):I1.
163. Gendelman R, Xing H, Mirzoeva OK, Sarde P, Curtis C, Feiler HS, et al. Bayesian network inference modeling identifies TRIB1 as a novel regulator of cell-cycle progression and survival in cancer cells. Cancer Res. 2017;77(7):1575–85.
164. Strickler JH, Loree JM, Ahronian LG, Parikh AR, Niedzwiecki D, Pereira AAL, et al. Genomic landscape of cell-free DNA in patients with colorectal cancer. Cancer Discov. 2018;8:164–73.
165. Diaz LA Jr, Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature. 2012;486(7404):537–40.
166. Siravegna G, Mussolin B, Buscarino M, Corti G, Cassingena A, Crisafulli G, et al. Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients. Nat Med. 2015;21(7):795–801.
167. Navin NE, Hicks J. Tracing the tumor lineage. Mol Oncol. 2010;4(3):267–83.
168. Greaves M. Evolutionary determinants of cancer. Cancer Discov. 2015;5(8):806–20.
169. Cao W, Wu W, Yan M, Tian F, Ma C, Zhang Q, et al. Multiple region whole-exome sequencing reveals dramatically evolving intratumor genomic heterogeneity in esophageal squamous cell carcinoma. Oncogene. 2015;4:e175.
170. Uchi R, Takahashi Y, Niida A, Shimamura T, Hirata H, Sugimachi K, et al. Integrated multiregional analysis proposing a new model of colorectal cancer evolution. PLoS Genet. 2016;12(2):e1005778.
171. Shu Y, Wu X, Tong X, Wang X, Chang Z, Mao Y, et al. Circulating tumor DNA mutation profiling by targeted next generation sequencing provides guidance for personalized treatments in multiple cancer types. Sci Rep. 2017;7(1):583.
172. Gao J, Wang H, Zang W, Li B, Rao G, Li L, et al. Circulating tumor DNA functions as an alternative for tissue to overcome tumor heterogeneity in advanced gastric cancer. Cancer Sci. 2017;108(9):1881–7.
173. Husain H, Velculescu VE. Cancer DNA in the circulation: the liquid biopsy. JAMA. 2017;318(13):1272–4.
174. Li Y, Wu S, Bai F. Molecular characterization of circulating tumor cells-from bench to bedside. Semin Cell Dev Biol. 2018;75:88–97.
175. Razavi P, Li B, Abida W, Aravanis A, Jung B, Shen R. Performance of a high-intensity 508-gene circulating-tumor DNA (ctDNA) assay in patients with metastatic breast, lung, and prostate cancer. J Clin Oncol. 2017;35(18_suppl):11516.
176. Razavi P, Li B, Hou C, Shen R, Venn O, Lim R. Cell-free DNA (cfDNA) mutations from clonal hematopoiesis: implications for interpretation of liquid biopsy tests. J Clin Oncol. 2017;35(15_suppl):11526.
177. Eisenberg R, Varmus H. Insurance for broad genomic tests in oncology. Science. 2017;358(6367):1133–4.

Preserving Fertility in Patients with Gastrointestinal Cancers

35

Didem Tunalı, Sule Yildiz Oğuz, Ugur Selek, Emre Balik, Senol Tonyali, Sertac Yazici, and Özgür Öktem

Introduction

Millions of young women are diagnosed with cancer every year, and exposed to cytotoxic chemotherapy regimens and radiation [1]. Unfortunately, modern combination regimens of chemotherapy and radiotherapy consequently have negative impacts on both reproduction functions and quality of life for both females and males.

Premature gonadal failure, infertility, and other poor reproductive outcomes of subsequent cancer therapies are being recognized as long-term consequences of cancer therapies. Therefore, preservation of gonadal function and fertility has become one of the major quality of life issues for cancer survivors at reproductive ages. In addition, sphincter dysfunction and other issues related to permanent colostomy are other factors that adversely affect the quality of daily and sexual life in the surviving patients with colorectal cancers. In this chapter, we will review the impact of treatment modalities on reproductive functions of both female and male patients diagnosed with gastrointestinal cancers and summarize the current established and experimental strategies to preserve their fertility and reproductive function.

D. Tunalı
Department of Internal Medicine, Division of Medical Oncology, Koc University School of Medicine, Topkapı, Istanbul, Turkey

S. Y. Oğuz · Ö. Öktem (✉)
Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, and Comprehensive Cancer Care and Fertility Preservation Programs, Koc University School of Medicine, Topkapi, Istanbul, Turkey
e-mail: ooktem@ku.edu.tr

U. Selek
Department of Radiation Oncology, Koc University School of Medicine, Sariyer, Istanbul, Turkey

E. Balik
Department of Surgery, Koc University School of Medicine, Sariyer, Istanbul, Turkey

S. Tonyali
Department of Urology, Turkiye Yuksek Ihtisas Training and Research Hospital, Altındag, Ankara, Turkey

S. Yazici
Department of Urology, Hacettepe University School of Medicine, Altındağ, Ankara, Turkey

Incidence and Facts About Gastrointestinal Cancers

The numbers of new cases of invasive cancer of the gastrointestinal system (GIS) that were expected in the United States in 2017 by sex are shown in Table 35.1 [2] with estimated new diagnoses and estimated deaths.

According to US cancer statistics of 2017[1], the estimated number of newly diagnosed GI cancers was 310,440, and the number of GI cancer deaths was estimated to be 157,700 [2]. Among both sexes, colorectal cancers are the most common of the GI cancers, followed by pancreas and hepatobiliary tract cancers. Estimated death rates are comparable in both sexes. Therefore, more focus will be given to colorectal cancers.

Newly diagnosed cancer patients consider fertility preservation to be a critical issue [3, 4]. A trial in men showed that banking sperm was a positive factor for emotionally fighting with cancer, even though the sperm samples were never used for some patients [4]. The President's Cancer Panel in the United States recommends that all cancer patients who are in the reproductive period of their life should be informed about the risk of treatment-related infertility.

In a trial of patients between 20 and 40 years old who were diagnosed with colorectal cancer, only 34% of them were told about the fertility risks associated with treatment and the options for fertility preservation [5]. Patients receiving radiation were more often offered fertility preservation, because of the well-known risks of radiation therapy on reproductive organs. Age was an important factor for this discussion, being statistically important in males; however,

[1]The most recent data available at the time of this chapter's writing.

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_35

Table 35.1 Cancer statistics 2017 [2]

	Estimated new cases			Estimated deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
Digestive system	310,440	175,650	134,790	157,700	92,350	65,350
Esophagus	16,940	13,360	3580	15,690	12,720	2970
Stomach	28,000	17,750	10,250	10,960	6720	4240
Small intestine	10,190	5380	4810	1390	770	620
Colon	95,520	47,700	47,820	50,260	27,150	23,110
Rectum	39,910	23,720	16,190			
Anus, anal canal, and anorectum	8200	2950	5250	1100	450	650
Liver and intrahepatic bile duct	40,710	29,200	11,510	28,920	19,610	9310
Gallbladder and other biliary	11,740	5320	6420	3830	1630	2200
Pancreas	53,670	27,970	25,700	43,090	22,300	20,790
Other digestive organs	5560	2300	3260	2460	1000	1460

while it was also important in females, it was not statistically significant according to this trial [5].

So as a result, fertility preservation options should be discussed with patients and referral to fertility specialists should be done as required.

The Impact of Treatment Modalities for Gastrointestinal Tumors on Reproductive Organs

Females

The clinical manifestations of chemotherapy-induced ovarian damage may range from temporary menstrual irregularity to amenorrhea, infertility, and premature ovarian failure depending upon the extent of the damage in the ovarian follicle pool. Resting primordial follicles, the earliest form of follicles, constitute 90% of the follicle pool (ovarian reserve), with the remaining 10% belonging to the growing follicles at the primary stage and beyond [6]. The probability of developing such adverse reproductive outcomes depends on multiple factors such as the age and ovarian reserve of the patient, and the type, dose, and duration of the chemotherapy regimen. Younger patients (<age 40) have larger ovarian reserves (higher number of primordial follicles in their ovaries) and therefore are more likely to retain or regain menstrual function than those older than age 40 after exposure to chemotherapy drugs (22–56% vs. 11%) [7]. A chemotherapy agent that preferentially targets the primordial follicles may result in the diminishment or total exhaustion of ovarian reserve depending upon the toxicity, dose, and duration of the therapy. If the loss of ovarian function develops during or shortly after the completion of cancer therapy, it is termed acute ovarian failure (AOF). AOF generally reflects the destruction of the growing follicle fraction, especially antral follicles and preovulatory follicles, which are the main sources of sex steroid secretion. AOF may be reversible depending upon the extent of the damage in the follicle stockpile. But it should be remembered that return of menses does not guarantee a normal reproductive life span since the loss of primordial follicles may occur insidiously without any warning sign or menstrual abnormalities. This also explains why women with critically diminished ovarian reserves may continue to menstruate regularly. For survivors who retained or resumed ovarian function after the completion of cancer treatment, a subset will go on to experience menopause before age 40 and be classified as having premature menopause.

Males

Chemotherapy, surgery, and irradiation adversely affect testicular function by various mechanisms such as direct cytotoxic effect on the germ cells and traumatic injury of the testes and its vascular structures and innervations [8]. It has been shown that about 40–63% of men have impaired sperm quality (such as low count, poor motility, or abnormal morphology) at the time of cancer diagnosis [9]. The testis was found to be highly vulnerable to the toxic effects of chemotherapy and irradiation in all stages of a male's life. The risk of testicular dysfunction or failure is dependent on the type and dose of chemotherapeutic agent and duration of irradiation, and its manifestation varies from temporary oligozoospermia to permanent azoospermia depending upon the extent of the damage.

Cytotoxic effects of gonadotoxic treatment after puberty in males is an extensively studied issue. However, there is a paucity of information regarding the effects of these treatment modalities to immature testes. The most actively proliferating cells are more prone to the cytotoxic effects

of gonadotoxic treatment, thus the differentiating spermatogonia are most susceptible to these treatments. It has also been reported that less active stem cell poll might be depleted. The recovery of sperm production after cancer treatment is associated with the spermatogonial stem cell population and their differentiation ability. If the treatment does not kill spermatogonial stem cells, normal sperm production is usually achieved within 3 months after cancer treatment.

Long-term survivors of cancer (lymphoma, testicular cancer, colorectal cancer, etc.) are affected by long-term effects of chemotherapy.

Spermatogenesis is more affected by chemotherapy than is testosterone production because the germinal epithelium of testis is more sensitive to being destroyed by chemotherapy than are the Leydig cells. The degree of the damage of germinal epithelium of the testis is affected by the stage of the sexual maturation of the testis. Postpubertal testis is more sensitive to the deterioration of chemotherapy when compared with prepubertal testis [10]. The effects of chemotherapy on sperm production depend on both the drug type and drug dose [11–16].

Germinal Epithelium The cells in the seminiferous tubules of the germinal epithelium have the highest mitotic index and meiotic index, so they are the ones that are most affected by the toxic effects of chemotherapy [12, 17]. As a result of the kinetics of spermatogenesis, sperm counts begin to decrease within a few weeks of chemotherapy, and azoospermia occurs in 2–3 months [18, 19]. Chemotherapy is most toxic to rapidly proliferating type B spermatogonia because chemotherapy agents are acting on the sperm cells during cell division. Type B spermatogonia can be reproduced from the germinal stem cell layer.

But the severity and duration of gonadal damage is best related to the number of damaged stem cells (also called type A spermatogonia) [20]. Drugs that destroy the stem cells cause permanent infertility. When the stem cells within the tubules remain intact, spermatogenesis may recover approximately 12 weeks after chemotherapy.

Leydig Cells These cells are the ones that produce testosterone and they are less commonly affected by chemotherapy [11, 21, 22]. When there is Leydig cell abnormality, we observe low levels of testosterone and high levels of luteinizing hormone (LH) [22]. In a clinical trial of 35 male patients suffering from mild Leydig cell damage after chemotherapy, supplemental testosterone for 12 months showed no beneficial impact on the quality of life, lipids, or bone mineral density (BMD) [23]. However, in patients with hypogonadal testosterone levels, testosterone replacement is a reasonable option.

Chemotherapy and Other Systemic Therapies

Females

Chemotherapy agents have different gonadotoxic potentials depending upon their category and mode of action. Alkylating agents such as cyclophosphamide are the most toxic. They are followed in order of decreasing cytotoxicity by platinum drugs, topoisomerase inhibitors, taxanes, anthracyclines, and antimetabolite drugs (Table 35.2) [24–27]. Some of these drugs are cell cycle specific and some are not. In the former category, methotrexate and 5-fluorouracil (5-FU) exert their cytotoxic effects in the S phase during DNA replication, while vinorelbine and taxanes (also called mitotic inhibitors) impair mitotic cell division by disrupting polymerization and depolymerization of mitotic spindles, respectively. In contrast, cell cycle nonspecific agents such as cyclophosphamide, topoisomerase inhibitors, and antitumor antibiotics (anthracyclines) damage cells at every stage of the cell cycle, causing a more widespread ovarian damage. Resting primordial follicles appear to be more sensitive to cyclophosphamide-induced gonadotoxicity than growing follicles at primary stage and beyond [28]. Chemotherapy agents that act in a cell cycle specific manner, such as 5-FU and methotrexate, are less harmful to primordial follicles and are more likely to damage the fraction of growing follicles with higher metabolic demand such as preantral and antral cohorts in the ovary. Unfortunately, there is a paucity of data in the literature that assesses the gonadotoxic potentials of chemotherapy regimens used in the treatment of GIS tumors.

Oxaliplatin, 5-FU, capecitabine, irinotecan, cetuximab, bevacizumab, panitumumab, or aflibercept are used preoperatively or postoperatively in the treatment of colorectal cancers [29–32].

Cytotoxic Drugs

Among the aforementioned drugs, oxaliplatin is more detrimental to the ovary than the others. Oxaliplatin and other platinum-containing cancer drugs such as cisplatin (cisplatin is widely used for gastric cancer treatment) cause the DNA strands to cross link, which impairs DNA replication and mitosis, and ultimately induces apoptosis.

5-FU and its orally administered prodrug form, capecitabine, have the least or no ovarian toxicity at all [1]. Oxaliplatin is combined with 5-FU and leucovorin in what is known as the FOLFOX regimen. In a study of 73 females under age 50 who were treated with this regimen, 41% (n = 20) experienced amenorrhea during chemotherapy and 16% had persistent amenorrhea 1 year after completion of chemotherapy [33]. The incidence of amenorrhea during chemotherapy trended higher in patients older than 40 compared

Table 35.2 Chemotherapy drugs categorized according to their mechanism of action and effect on ovarian functions [24–27]

Category	Group	Gonadotoxicity
Antimetabolites	*Folic acid antagonists* (aminopterin, methotrexate, pemetrexed, raltitrexed) *Purine analogs* (cladribine, clofarabine, fludarabine, mercaptopurine, pentostatin, thioguanine) *Pyrimidine analogs* (cytarabine, decitabine, fluorouracil/capecitabine, floxuridine, gemcitabine, enocitabine, sapacitabine)	Mild toxicity Block DNA synthesis Cell cycle specific (S phase, DNA synthesis) Possibly more toxic on the growing fraction of the follicle pool at preantral stage and onward due to their higher mitotic rates and metabolic demands
Alkylating agents	*Nitrogen mustards* (chlorambucil, chlormethine, cyclophosphamide, ifosfamide, melphalan, bendamustine, trofosfamide, uramustine) *Nitrosoureas* (carmustine, fotemustine, lomustine, nimustine, prednimustine, ranimustine, semustine, streptozocin) *Platinum (alkylating-like)* (carboplatin, cisplatin, nedaplatin, oxaliplatin, triplatin tetranitrate, satraplatin) *Alkyl sulfonates* (busulfan, mannosulfan, treosulfan) Hydrazines: (procarbazine) Triazenes: (dacarbazine, temozolomide) *Aziridines* (carboquone, ThioTEPA, triaziquone, triethylenemelamine)	Alkylating chemotherapeutics are the most gonadotoxic agents Targets cells at different stages of cell cycle (not cell cycle specific). They exert selectively more toxicity on resting primordial follicles (cyclophoshamide) High-dose cyclophosphamide (200 mg/kg) is frequently used as conditioning therapy before bone marrow transplantation (BMT) Used as the first-line therapy for leukemia, lymphoma, and other pediatric tumors
Spindle poisons Mitotic inhibitor	*Taxanes* (docetaxel, larotaxel, ortataxel, paclitaxel, tesetaxel) *Vinca* (vinblastine, vincristine, vinflunine, vindesine, vinorelbine, ixabepilone)	Less cytotoxic than alkylating agents and platinum group Taxanes function as mitotic inhibitor by stabilizing microtubules and as a result, interfering with the normal breakdown of microtubules during cell division The vinca alkaloids inhibit assembly of microtubule structures. Disruption of the microtubules arrests mitosis in metaphase. Therefore, the vinca alkaloids affect all rapidly dividing cell types including cancer cells, but also those of intestinal epithelium and bone marrow No ovarian toxicity was documented in a small number of women receiving vincristine [24]
Cytotoxic Antitumor antibiotics	*Anthracycline family* (aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, amrubicin, pirarubicin, mitoxantrone, pixantrone, valrubicin, zorubicin) *Streptomyces* (actinomycin, bleomycin, mitomycin, plicamycin)—hydroxyurea	Anthracyclines inhibit DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand, thus preventing the replication of rapidly growing cancer cells They also create iron-mediated free oxygen radicals that damage the DNA and cell membranes They follow alkylating and platinum compounds in ovarian toxicity They inhibit transcription by binding DNA at the transcription initiation complex and preventing elongation by RNA polymerase Their gonadal toxicity profiles are similar to anthracyclins
Topoisomerase inhibitors	*Camptotheca* (camptothecin, topotecan, irinotecan, rubitecan, belotecan) *Podophyllum*: (etoposide, teniposide)	They form a ternary complex with DNA and the topoisomerase I enzyme, preventing re-ligation of the DNA strands. This causes errors in DNA synthesis and promotes apoptosis of the cancer cell Limited data suggest moderate ovarian toxicity [25–27]
Monoclonal antibodies	*Receptor tyrosine kinase inhibitors* (cetuximab, panitumumab, trastuzumab)—CD20 (rituximab) *Others* (alemtuzumab, bevacizumab, edrecolomab, gemtuzumab)	No data on ovarian toxicity
Tyrosine kinase inhibitors	Axitinib, bosutinib, cediranib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sorafenib, sunitinib, vandetanib	No data on ovarian toxicity
Cyclin-dependent kinase inhibitors	Alvocidib, seliciclib	No data on ovarian toxicity
Others	Fusion protein (aflibercept), denileukin diftitox	No data on ovarian toxicity
Photosensitizers	Aminolevulinic acid, efaproxiral, methyl aminolevulinate, porfimer sodium, talaporfin, temoporfin, verteporfin	No data on ovarian toxicity
Ungrouped	Retinoids (alitretinoin, tretinoin), anagrelide, arsenic trioxide, asparaginase (pegaspargase), atrasentan, bortezomib, carmofur, celecoxib, demecolcine, elesclomol, elsamitrucin, etoglucid, lonidamine, lucanthone, masoprocol, mitobronitol, mitoguazone, mitotane, oblimersen, omacetaxine, sitimagene ceradenovec, tegafur, testolactone, tiazofurine, tipifarnib, vorinostat	No data on ovarian toxicity

with patients aged 40 and younger (59% vs. 31%; $p = 0.075$). There was no statistically significant difference in persistent amenorrhea between the two age groups (24% vs. 13%; $p = 0.42$) [33]. A similar study compared the incidence of amenorrhea in 95 premenopausal women with colon carcinoma and 67 premenopausal women with rectal carcinoma aged 40 years or younger [34].

FOLFOX (5-fluorouracil, calcium leucovorin, oxaliplatin), XELOX (capecitabine, oxaliplatin), or capecitabine alone are used as adjuvant treatment in colorectal cancer patients after optimal surgery. Patients with stage II or III rectal cancer were treated with neoadjuvant or adjuvant chemoradiotherapy with 5-FU or capecitabine. The incidence of amenorrhea was no different between the women receiving adjuvant FOLFOX and those receiving XELOX (4.9% vs. 5.6%; $p = 0.913$). Of the 51 patients with rectal cancer, 48 patients (94.1%) experienced a cessation of menses during chemoradiotherapy, and no patient resumed menses after the completion of chemoradiotherapy. Only three (5.9%) patients maintained menses after the completion of treatment. Thus, the incidence of amenorrhea was significantly lower in patients with colon cancer (4.2%; 3 of 72) when compared with patients with rectal cancer (94.1%; 48 of 51) ($p < 0.01$) [34].

Limited data on the gonadotoxicity of irinotecan and other topoisomerases suggest that they are more toxic to the ovary than antimetabolite drugs. Irinotecan induced apoptosis of the granulosa cells of the ovarian follicles by upregulating FasL expression [35, 36].

Docetaxel, cisplatin, oxaliplatin, 5-FU, capecitabine, epirubicin, and irinotecan are commonly used before or after surgery in the treatment of gastric carcinomas [37]. Cisplatin and oxaliplatin pose a greater risk of ovarian damage than other drugs. Data on ovarian toxicity of docetaxel is largely derived from breast cancer patients receiving taxane-based chemotherapy protocols. For instance, the PACS01 trial—comparing six cycles of fluorouracil, epirubicin, and cyclophosphamide (6FEC) versus three cycles of FEC followed by three cycles of docetaxel (3FEC/3D)—showed that patients receiving the 6FEC versus the 3FEC/3D had similar rates of amenorrhea at the end of chemotherapy (93% vs. 92.8%) [38]. However, 1 year later more patients in the 3FEC/3D arm than in the 6FEC arm recovered menses (35.5% vs. 23.7%, $p < 0.05$) and had premenopausal hormone levels (43% vs. 29%). There was an increased incidence of reversible amenorrhea (i.e., resumption of menses or recovery of premenopausal hormone values) in the taxane-containing arm for patients aged more than 40 years (20.5 vs. 10.5%, $p = 0.025$), whereas there was no difference in patients below 40 years of age, suggesting that the addition of docetaxel to the FEC regimen may increase the gonadotoxic potential of the regimen in older patients. The Breast Cancer International Research Group (BCIRG) 01 trial showed that the incidence of amenorrhea was higher in the docetaxel, doxorubicin, and cyclophosphamide (TAC) arm compared with the fluorouracil, doxorubicin, and cyclophosphamide (FAC) arm (51.4% vs. 32.8%, respectively) [39]. In the light of these data, it can be concluded that docetaxel has a moderate gonadotoxic potential.

Similarly to other anthracyclines, epirubicin acts by intercalating DNA strands. Intercalation results in complex formation that inhibits DNA and RNA synthesis. It also triggers DNA cleavage by topoisomerase II, resulting in mechanisms that lead to cell death. Binding to cell membranes and plasma proteins may be involved in the compound's cytotoxic effects. Epirubicin also generates free radicals that cause cell and DNA damage [1]. Anthracyclines are far less toxic than alkylating agents and platinum drugs. Amenorrhea was reported by 80% of premenopausal patients who received anthracycline-based regimens for breast cancer. However, none of the patients under 30 years of age had menstrual abnormalities, whereas 96% of those 40–49 years of age developed amenorrhea. Amenorrhea was permanent for most women over 40, but it was reversible for 50% of patients under 40 years of age [40].

Monoclonal Antibodies

Monoclonal antibodies are used in the metastatic period of GI cancers. Cetuximab and panitumumab are monoclonal antibodies that inhibit epidermal growth factor receptor (EGFR). Bevacizumab and aflibercept are inhibitors of vascular endothelial growth factor (VEGF) pathway. In 2011 the US Food and Drug Administration (FDA) added a warning label to bevacizumab because of its ovarian toxicity, which was documented in a prospective study conducted by the developer company. In that study 179 premenopausal women were randomized to receive chemotherapy with or without bevacizumab; the incidence of ovarian failure was higher in the bevacizumab arm (34%) compared to the control arm (2%). After discontinuation of bevacizumab and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these bevacizumab-treated patients [41].

Receptor Tyrosine Kinase Inhibitors

Imatinib mesylate is a small molecule tyrosine kinase inhibitor (TKI) that targets BCR-ABL and c-kit and is used in the treatment of gastrointestinal stromal tumors (GISTs) in GI cancers. There are some case reports that show gonadotoxic effects of this drug on human ovary [42, 43]. Two animal studies assessing the protective role of this drug against cisplatin-induced ovarian toxicity yielded conflicting results [44, 45]. A recent in vitro study utilizing human ovarian tissue samples and granulosa cells showed that imatinib had gonadotoxic effects on human ovary and did not confer any protection against cisplatin-induced follicle death [46]. Well-designed clinical studies are needed to test its gonadotoxic effects.

Males

The chemotherapy agents that are most deleterious for male fertility are alkylating agents (cyclophosphamide, chlorambucil, cisplatin, and busulfan). Among these drugs, cisplatin is the one that we mostly use in GI cancers—especially in gastric, pancreatic, and biliary tract cancers. Oxaliplatin is widely used in regimens for colorectal, gastric, pancreatic, and biliary cancers. These drugs have a risk of permanent infertility with cumulative dose ranges [11, 17, 21, 47, 48]. Infertility with alkylating agents is dose and age dependent. We will discuss each drug below.

For many cases, azoospermia or oligospermia is temporary after chemotherapy; sperm production recovers within months to as long as 4 years following therapy. Sperm counts do appear to be lower after chemotherapy, and there can be damage to the DNA of sperm after chemotherapy. This damage is repaired by 2 years after therapy, although the exact time for repair is not known. That is why men are typically counseled to wait 2 years after therapy before fathering a child.

In prepubertal males, some chemotherapeutics impair fertility; fortunately, in many cases, azoospermia is not permanent, and after a variable period of time, spermatogenesis comes back [20, 49]. But most of the data about the impact of chemotherapy on spermatogenesis comes from the studies including adult patients [50, 51].

Cytotoxic Drugs

Chemotherapy drugs that have the highest risk of infertility in males are actinomycin D, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide (Cytoxan®), cytarabine, ifosfamide, lomustine, melphalan, nitrogen mustard (mechlorethamine), and procarbazine (Table 35.3) [52]. Higher doses of these drugs may cause permanent infertility, and combination regimens may cause more deterioration of fertility. The risks of permanent infertility are higher when males are treated with a combination of chemotherapy and radiotherapy to the abdominal region or pelvis.

Some drugs have a lower risk of infertility in males when they are given in low to moderate doses 5-fluorouracil (5-FU), 6-mercaptopurine (6-MP), bleomycin, cytarabine (Cytosar®), dacarbazine, daunorubicin (Daunomycin®), doxorubicin (Adriamycin®), epirubicin, etoposide (VP-16), fludarabine, methotrexate, mitoxantrone, thioguanine (6-TG), thiotepa, vinblastine (Velban®), and vincristine (Oncovin®).

Cisplatin, oxaliplatin, 5-FU, capecitabine, and irinotecan are the drugs that we use in the treatment of GI cancers. The regimens are FOLFOX, XELOX, FOLFIRI (leucovorin, 5-FU, irinotecan), FOLFIRINOX (leucovorin, 5-FU, irinotecan, oxaliplatin), and DCF (docetaxel, cisplatin, 5-FU) are the combination regimens that we generally prefer to use for the GI cancers.

Table 35.3 Chemotherapy drugs with highest risk of infertility in males

Chemotherapy (dose to cause effect)	Known effect on sperm count
Chlorambucil (1.4 g/m^2)	Prolonged or permanent azoospermia
Cyclophosphamide (19 g/m^2)	
Procarbazine (4 g/m^2)	
Melphalan (140 mg/m^2)	
Cisplatin (500 mg/m^2)	
BCNU (1 g/m^2)	Azoospermia in adulthood if treated before puberty
CCNU (500 mg/m^2)	
Busulfan (600 mg/m^2)	Azoospermia likely, and these are often given with other highly sterilizing agents, adding to the effect of them
Ifosfamide (42 g/m^2)	
BCNU (300 mg/m^2)	
Nitrogen mustard	
Actinomycin D	
Doxorubicin (770 mg/m^2)	When used alone, causes only temporary reductions in sperm count. In combination with the above agents, may be additive in causing azoospermia
Thiotepa (400 mg/m^2)	
Cytarabine (1 g/m^2)	
Vinblastine (50 g/m^2)	
Vincristine (8 g/m^2)	
Amsacrine	When used in conventional regimens, cause only temporary reductions in sperm count. In combination with the above agents, may be additive in causing azoospermia
Bleomycin	
Dacarbazine	
Daunorubicin	
Epirubicin	
Etoposide	
Fludarabine	
Fluorouracil	
6-mercaptopurine	
Methotrexate	
Mitoxantrone	
Thioguanine	

Adapted from [52]

Oxaliplatin is a phase nonspecific alkylating-like platinum agent just like cisplatin. In a trial, eight male patients receiving oxaliplatin (two patients were metastatic and additionally received bevacizumab) were treated with XELOX or FOLFOX regimens. The median age for the men was 38 years (33–41 years). After treatment the male patients had follicle-stimulating hormone (FSH) elevation and inhibin-B depletion, which means that spermatogenesis was affected. However, their testosterone levels transiently increased, and sex hormone-binding globulin (SHBG) levels were not altered, indicating that their Leydig cells were functional [53].

5-FU is a cell cycle specific (S phase, DNA synthesis) drug and widely used in combination with other drugs in almost all of the GI cancer treatment regimens. A trial with rats showed that 5-FU decreased the number of spermatozoa in a time- and dose-dependent manner. 5-FU decreases the number of spermatozoa by inhibition of cell multiplication and interference with the sperm differentiation process [54]. There is a negative linear correlation between the sperm count and 5-FU exposure. The deepest fall in the sperm

count occurs on the 35th day of 5-FU administration. This points out that the cells that are most sensitive to 5-FU are the ones belonging to the spermatogonial cell population and the toxicity of 5-FU rises over time [54].

Irinotecan is an S phase-specific inhibitor of topoisomerase I. Irinotecan prevents ligation of the DNA strand by binding to topoisomerase I-DNA complex, and causes double-strand DNA breakage and cell death, which impairs cell proliferation. In vivo, irinotecan is converted into its active metabolite, 7-ethyl-10-hydroxycamptothecan (SN38), and that is a thousand times more cytotoxic than irinotecan itself [55]. In a mouse model trial, it was shown that irinotecan-metabolite SN38 resulted in damage to testes, significantly affecting germ cells following exposure to clinically relevant concentrations of SN38. Interestingly, in contrast, it had only minor effects on the ovaries and had no effects on ovarian germ cell number even following exposure to 50 times higher concentrations of SN38 than that reported to date in patients following irinotecan administration [56]. In this trial, prepubertal mice were used and this model shows that germ cells in the ovaries of prepubertal girls may be less susceptible to damage by irinotecan administration than those in the testes of prepubertal boys [56].

Men undergoing chemotherapy including irinotecan are generally warned of a possible impairment in sperm production, [57] despite the fact that there are no data available showing the effect of irinotecan on spermatogenesis.

Cisplatin is a phase nonspecific alkylating-like platinum agent. As we mentioned earlier, alkylating chemotherapeutics are the most gonadotoxic agents. Cumulative doses >400 mg/m^2 cisplatin cause permanent infertility in 50% of men, but lower doses may not cause long-term impaired fertility [16]. In a trial of germ cell tumors, with one group receiving chemotherapy and the other group not receiving chemotherapy, it was shown that serum FSH and LH levels showed significant differences in the group of patients who received cumulative cisplatin above 400 mg/m^2. These patients were also the ones with azoospermia [18]. Yet, some studies have found no significant differences in FSH and LH levels after 2 years of chemotherapy including total cisplatin less than 400 mg/m^2 [58].

Unfortunately, permanent azoospermia may happen in more than 50% of the patients who received total cisplatin of more than 600 mg/m^2 [59]. It is difficult to predict the time and dose dependence of recovery in patients receiving cisplatin, because in a trial with follow-up of 8 years, some of the patients achieved a recovery of spermatogenesis even though they received more than 600 mg/m^2 cisplatin [60].

The existing trials with gemcitabine on male fertility are only the ones with animal models. In one of these trials, there was a reduction in height, perimeter, and area of seminiferous tubular morphology of Swiss albino mice; the sertoli cell number of the mice also decreased. Sperms have shown banana heading and lost their normal look. The effects were partially reversible at the end of 2 months for sperms and permanent after 2 months for sertoli cells. Consequently, gemcitabine affects the process of spermatogenesis adversely in a dose- and time-dependent manner; the effects are partially reversible [61].

Monoclonal Antibodies

Bavcizumab can impair fertility in women, but there are no studies showing reduction in male fertility.

When added to cisplatin, cetuximab exacerbated the effects of cisplatin on testicular parameters: including testis and epididymis weights, epididymal-spermatozoa total motile count, anti-Müllerian hormone (AMH) concentration, meiosis, and apoptosis. In fact, cetuximab had a mild effect on testicular reserve, but when added to cisplatin it exacerbated cisplatin-induced testicular toxicity [62].

Radiation Therapy

Spermatogenesis is highly vulnerable to damage even at very low doses of irradiation. However, the extent of the damage depends on the dose, treatment area, and fractionation schedule. Recovery of spermatogenesis takes place by means of type A spermatogonia within 30 months following radiation with 2–3 Gy. Permanent damage in spermatogenesis and permanent azoospermia may occur at doses exceeding 6 Gy.

The utility of radiotherapy in rectal cancers was questioned via two important meta-analyses, and its robust role has been verified [63, 64]. The Colorectal Cancer Collaborative Group (CCCG) evaluated 22 trials including 8500 cases and concluded that both preoperative (46% decrement in local recurrence) and postoperative (37% decrement in local recurrence) radiotherapies provided local control benefit over surgery alone [63]. The Swedish Council of Technology Assessment in Health Care reported their analysis of 42 randomized studies, 3 meta-analyses, and 36 prospective and 7 retrospective studies including 25,000 cases and concluded that the preoperative radiotherapy approach ensured better local control than postoperative radiotherapy [64]. The point to be remarked upon is the significant 10% increase in overall survival with preoperative single-modality radiotherapy while the postoperative radiotherapy approach failed to reach significance without chemotherapy.

The first randomized study demonstrating overall survival benefit for all cohorts with preoperative radiotherapy alone was the Swedish trial [65]. Clinically resectable 1168 rectal cancer patients were randomized to 25 Gy (5 Gy fractions in 1 week) preoperative radiotherapy and immediate surgery in 1 week versus surgery alone, and revealed the local control and overall survival benefit with preoperative radiotherapy. In the era of total mesorectal excision (TME), a Dutch trial evaluated the same protocol and pointed out the significant

decrement in local failures (surgery alone 8.2% vs. radiotherapy + surgery 2.4%) while noting longer a follow-up requirement for survival [66]. Swedish trials [67–69] comparing surgery alone with neoadjuvant short-course radiotherapy and immediate surgery identified that radiotherapy reduced local recurrence ranging from 52% to 65% as well as resulted in an absolute benefit of 8% in overall survival at 13 years [69]. Even in the TME era, randomized studies of the Dutch TME trial [70, 71] and Medical Research Council (MRC) CR07 trial [72] showed an approximately 50%–60% relative reduction of local recurrence after short-course preoperative radiotherapy with an absolute local control benefit of 5%–6%, while no overall survival benefit with radiation was found.

Preoperative radiotherapy has been shown to be preferable to postoperative radiotherapy with lower rates of local relapse and toxicity [73, 74]. The regimens differ in the preoperative radiotherapy approach. While a short course is preferred in Northern Europe, a long course is favored in Southern Europe and America. Neoadjuvant radiotherapy has been developed to offer two regimens that could be accepted as standard for resectable rectal cancer: short-course 25 Gy (5 × 5 Gy) radiation therapy alone and long-course chemoradiation therapy (CRT).

The literature was lacking randomized trials comparing neoadjuvant short-course radiotherapy with neoadjuvant chemoradiotherapy for T3 cancers until the results of 2 trials questioning this dilemma [75–79]: (1) a Polish study evaluating the difference in rates of sphincter-preserving surgery between the long-course chemoradiation and short-course radiotherapy, and (2) an Australian study evaluating differences in local recurrence rates between these arms. Both trials demonstrated significantly increased early radiation toxicity in the chemoradiation group (grade 3–4 acute toxicity rates, Polish, 18% vs. 3%; Australian, 28% vs. 1.9%), which turned into improved adherence to the protocol in short-course radiation-only arms. Interesting in the Polish trial were the similar sphincter-preservation rates in both arms (short: 61% and long: 58%) and lower local recurrence rates in the short arm (short: 10.6% and long: 15.6%). Although the follow-up is still limited, no significant differences were observed between the randomized groups regarding survival, postoperative complications, late toxicity rates (severe late toxicity, Polish: 10.1% vs. 7.1%; Australian: 7.6% vs. 8.8%), quality of life, and anorectal and sexual functions in males and females.

The recent phase III Polish II trial for cT4 or fixed cT3 rectal cancer investigated the comparison of long-course preoperative chemoradiation of 50.4 Gy in 28 fractions combined with two 5-day cycles of bolus 5-FU 325 mg/m^2/day and leucovorin 20 mg/m^2/day during the first and fifth week of irradiation along with 5 infusions of oxaliplatin 50 mg/m^2 once weekly versus short course 5 × 5 Gy and 3 cycles of consolidation FOLFOX4 chemotherapy [80]. Bujko et al. revealed no differences in local efficacy between both arms but an improved overall survival and lower acute toxicity for the 5× 5 Gy schedule with consolidation chemotherapy [80]. The RAPIDO phase 3 trial is open to accrual for locally advanced rectal cancer randomizing a standard arm of chemoradiation (1.8 Gy × 25 or 2 Gy × 25 with capecitabine) preoperatively, followed by selective postoperative adjuvant chemotherapy of eight cycles of CAPOX (capecitabine and oxaliplatin) versus short-course radiotherapy followed by neoadjuvant six cycles of CAPOX chemotherapy [81].

Neoadjuvant therapy also has been investigated to be a total preoperative therapy before surgery with upfront rather than adjuvant chemotherapy to further improve outcomes by addressing possible micrometastatic disease as well as the primary tumor. Two phase II studies, UK and Spain trials, have evaluated induction chemotherapy followed by CRT before surgery in high-risk patients based on magnetic resonance imaging (MRI) for extent of extramural tumor and risk of circumferential resection margin positivity [82, 83]. Induction CAPOX chemotherapy before CRT in the UK EXPERT and Spanish GCR-3 trials had similar pathological complete response (pCR) and complete resection rates in comparison to postoperative adjuvant CAPOX, while more favorable compliance and toxicity profiles were achieved [83, 84]. Similarly, the Memorial Sloan Kettering Cancer Center (MSKCC) experience of total neoadjuvant radiotherapy with FOLFOX and chemoradiation followed by planned TME resulted in a considerable rate of pCR, and delivery of planned therapy, in addition to offering a very selective decent stand for possible nonoperative management [85]. mFOLFOX6 chemotherapy after concurrent chemoradiation before TME has also shown a potential to increase the pCR up to 38% [86].

The recently proposed NRG-GI002 phase II clinical trial platform will be randomizing a phase II modular clinical trial utilizing total neoadjuvant therapy with parallel experimental arms [87].

Females

Ionizing radiation and chemotherapy agents induce genomic damage and apoptosis in both oocytes and the surrounding granulosa cells, culminating in apoptotic death of the follicular apparatus [1, 88].

The direct action of radiation on DNA is the predominant mechanism of damage for particle radiation. There are also indirect actions that come from the interaction of radiation with other substances in the cell, such as water leading to the formation of free radicals and DNA damage. This mechanism is particularly true for sparsely ionizing radiation such as X-rays. Gonadal damage occurs by direct exposure to

radiation such as in the case of pelvic or low abdominal or lumbo-sacral spinal irradiation [89]. Furthermore, scatter radiation may cause significant damage even if the gonads are outside the radiation field. The risk of premature ovarian failure is higher with increasing radiation doses. Single doses appear to be more toxic than fractionated doses [90]. The dose required to induce permanent ovarian failure would vary from 20.3 Gy at birth to 14.3 Gy at 30 years [91]. In contrast to chemotherapy, uterine function is also often irreversibly compromised by radiation. Radiation-induced damage to uterine vascular and muscular structures result in decreased uterine blood flow, reduced uterine volume, decreased endometrial thickness, and loss of distensibility, and can potentially lead to infertility and adverse pregnancy outcomes such as miscarriages, still births, fetal growth restrictions, preeclampsia, and preterm deliveries in the survivors exposed to uterine radiation during childhood [89, 92–94].

Males

Radiotherapy for rectal cancer has been shown to be associated with reduced serum testosterone and increased FSH and LH [95]. Abdominal or pelvic radiotherapy in men bears the potential risk of scattered doses to the testes, which are outside of the treatment volume, causing impairment of their fertility [96]; measurements on anthropomorphic phantoms and thermoluminescent dosimetry measures on patients determined the magnitude of the scattered testicular doses (in four-field treatment with anterior-posterior and two lateral parallel pairs) to be approximately 1–2% of the target dose [96]. The risk of infertility after pelvic radiation depends on the testicular doses. Doses as small as 0.1 Gy would lead to decreased sperm counts, whereas doses of 1.5–4 Gy would possibly result in permanent sterility as spermatozoa seem not to tolerate irradiation doses higher than 6 Gy [97]. If total gonadal dose in any kind of scatter in pelvic radiotherapy exceeds 1.5 Gy, irreversible azoospermia is at stake [98]. The Leydig cells, responsible for testosterone production, are less sensitive to radiation effects, but start to be damaged by doses higher than 15–20 Gy in prepubescent males and above 30 Gy in mature males [97]. If the testicular dose is not high enough for permanent azoospermia, sperm counts are generally at their lowest in 4–6 months after treatment while they are expected to return to pretreatment levels in most males 10–24 months after treatment—possibly longer with higher doses. The treatment position of pelvic radiotherapy was also shown to be effective on testicular doses in patients with rectal carcinoma, and supine four-field pelvic radiotherapy seemed to provide lesser testicular doses to prone four-fields and prone three-fields in male patients with rectal carcinoma receiving 45 Gy pelvic radiotherapy [99]. Mean LH and FSH levels were shown to significantly increase after pelvic therapy (350%/185% of the pretreatment values) with a decrease in testosterone levels, along with the mean cumulative radiation exposure to the testicles, which was up to 7.1% of the prescribed dose [100]. Most of the gonadal dose was delivered by the posterior-anterior field due to the divergence of the beam toward the testicles in the basic three-dimensional approach. Testicular dose during rectal cancer radiotherapy can be defined as a dose constraint to decrease the scattered dose for better recovery of spermatogenesis with total doses below 100 cGy [101]. Modern radiotherapy series can achieve acceptable testicular doses. The median planned mean total dose for short-course radiotherapy (prescribed dose of 25 Gy, 5 × 5 Gy) was 0.57 Gy (range 0.06–14.37 Gy) and 0.81 Gy (range 0.36–10.80 Gy) for long-course radiotherapy (prescribed dose of 50 Gy, 25 × 2 Gy or 50.4 Gy, 28 × 1.8 Gy), which encourages chances of better recovery of spermatogenesis after radiotherapy [102, 103].

Different groups have studied rectal cancer radiotherapy based on the amount of small bowel receiving intermediate- and low-doses of radiation and correlation between the rates of severe diarrhea [104–106], revealing that a strong dose-volume relationship existed for the occurrence of Grade 3 acute small bowel toxicity in patients receiving preoperative radiochemotherapy. Consequently, a great interest has arisen to use highly conformal treatment approaches, such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc treatment (VMAT), delivering a highly conformal target dose while minimizing the dose to organ at risks (OAR). Numerous studies of the locally advanced rectal cancers have been working on different treatment approaches and comparisons including proton therapy, VMAT, IMRT and three-dimensional conformal radiotherapy (3DCRT) [107–112].

Clinical target volumes for conformal radiotherapy in rectal cancer have been documented as a Radiation Therapy Oncology Group (RTOG) Consensus Panel contouring atlas [113]:

- The radiotherapy field for the lower pelvis was defined as covering the entire mesorectum to the pelvic floor with a minimum of 2 cm caudad to gross rectal disease and not more than a few millimeters beyond the levator muscles.
- The field for mid pelvis was defined as pelvic sidewall musculature or the bone laterally, approximately 1 cm into the posterior bladder anteriorly, and at least the posterior portion of the internal obturator vessels between the external and internal iliacs in the mid pelvis.
- The field for the upper pelvis was defined as the rectosigmoid junction or 2 cm proximal to the superior extent of macroscopic disease in the rectum/peri-rectal nodes with the most cephalad aspect being bifurcation of the common iliac vessels into external/internal iliacs, at the approximate boney landmark of sacral promontory [113].

There has been documented a recent revised international contouring guideline based on delineation endorsed by international experts [114], which recommends consideration of anisotropic clinical target volume (CTV) margins anteriorly to account for bladder/uterus/seminal vesicles movement. Due to the fact that mesorectum, the fat around the rectum in the mid-low pelvis, being bounded anteriorly by the mesorectal fascia and by the posterior border of the anterior pelvic organs—such as prostate, seminal vesicles, bladder and penis bulb in men and the vagina and uterus in women—an anterior anisotropic internal margin is recommended to account for motion and/or volume variation for the bladder, uterus, and seminal vesicles [114].

Options of Fertility Preservation of Patients with Gastrointestinal Cancers

Females

Young women diagnosed with GIS cancers should be counseled for fertility preservation options because of the risk of infertility and premature ovarian failure associated with the use of chemotherapy and radiation at adjuvant settings. As stressed in the clinical guidelines by the American Society of Clinical Oncology (ASCO) and the practice committee opinion of the International Society for Fertility Preservation (ISFP) [115, 116], all cancer patients with interest in future fertility should be referred for consideration of fertility preservation. In a study performed by Strong et al., less than 20% of women of childbearing age who were given a diagnosis of colorectal cancer had documented counseling for posttreatment infertility and nearly 40% of the women had documented difficulty with pregnancy or changes in menses after treatment [117]. Even though some oncologists appear to routinely discuss the impact of treatment on potential fertility very few refer their patients to a reproductive endocrinologist, according to the results of the other survey conducted among 249 oncologists. When planning treatment, 30% rarely consider a woman's desire for fertility. Gynecologic oncologists were more likely to routinely consider fertility compared with other oncologists (93% vs. 60%). Gynecologic oncologists were also more likely to provide a less effective regimen to better preserve fertility compared to other oncologists (61% vs. 37%). Most oncologists (86%) would be willing to sacrifice less than a 5% reduction in disease-free survival if a regimen offered better fertility outcomes; only 36% felt that patients would be willing to sacrifice a >5% reduction in disease-free survival in order to preserve fertility [118]. These results underscore the critical role of oncologists in informing patients and parents about the risk of future infertility and other treatment-related adverse reproductive outcomes and to refer them to reproductive endocrinologists to discuss fertility preservation options.

Currently, embryo freezing and oocyte freezing are the established fertility preservation methods according to the most recent guidelines of the American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology (SART) [119]. Other options include ovarian tissue cryopreservation, the use of gonadotropin-releasing hormone agonist concurrent with chemotherapy administration, in vitro maturation (IVM), and ovarian transposition (Fig. 35.1).

Embryo Freezing

Embryo cryopreservation is the most established fertility preservation technique for patients with partners and a sufficient amount of time before cancer treatment. According to the data from the Society for Assisted Reproductive Technology and the European IVF Monitoring Program, the clinical pregnancy rate per frozen-thawed embryo exceeds 50% in women younger than 35 years [120, 121]. Cryopreservation employs standard ovarian stimulation techniques and has been used for two decades to store surplus embryos for in vitro fertilization (IVF) patients. It typically requires 10–14 days of ovarian

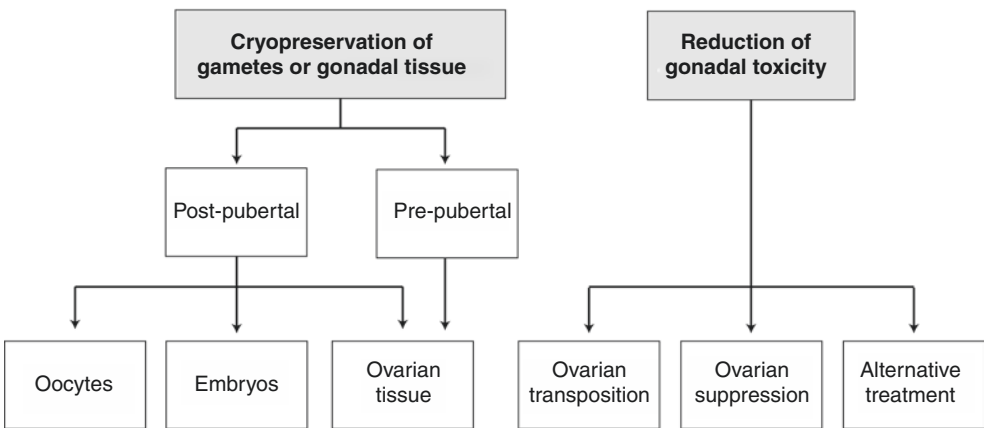


Fig. 35.1 Some female fertility preservation treatments

stimulation. Therefore, this strategy should be considered as the first option for patients with GIS cancer who have not completed childbearing, should they have enough time to undergo ovarian stimulation and do not have any contraindication for it.

Oocyte Freezing

Oocyte cryopreservation is ideal for women who do not have a partner and do not want to use donor sperm for fertility preservation. It does not require fertilization after egg retrieval, thus creation of unnecessary embryos can be prevented. Historically, the first live birth from a frozen human oocyte was reported in 1986 [122]. However, oocyte cryopreservation had been considered an experimental procedure until 2012. Previously, most oocytes were cryopreserved by slow freezing, and pregnancy rates with cryopreserved oocytes were too significantly low to be regarded as an established assisted reproduction technology (ART). However, significant advances in cryopreservation methods with a wide use of vitrification since 2006 have changed the course and status of oocyte cryopreservation in ART. With the dramatic increase in success with vitrification during recent years, the rates of ongoing pregnancy, top-quality embryo, embryo cleavage, and fertilization do not differ between the vitrified and the fresh oocyte groups [123]. When the data from 1998–2008 was analyzed, the oocyte survival rate was higher in the vitrified group (81%) compared to the slow-freezing group (68%). The live birth rate per embryo transfer (after fertilizing the thawed/warmed oocytes) was 14% and 34% in the slow-frozen and vitrified groups, respectively [124]. Cobo et al. reported that clinical pregnancy rates of IVF cycles with vitrified oocytes did not differ from those of fresh IVF cycles (55.4% vs. 55.6% per transfer) [125]. Nevertheless, the live birth rates per fresh mature oocyte and per vitrified oocyte have been low (4–6% vs. 4.5%) according to the results of several meta-analyses [125–127]. Moreover, the number of oocytes harvested and the live birth rate per oocyte further decrease with chronologic aging, especially after the age of 37. For instance, the live birth rate per mature oocyte is 4.47% for women under 37. From the age of 38 and onward, a significantly lower rate is noted, declining from 3.80% at the age of 38 to 0.78% at 43 [126].

At this point, one may ask "how many oocytes should be frozen to achieve a live birth?"' A recent longitudinal cohort multicentric study has provided an answer to this question by showing that more than 8 oocytes are required to improve live birth rates (22.6% versus 46.4%). When fewer oocytes are available in women aged >38 years, results are dramatically reduced (12.6% versus 27.5%) [128]. These figures are extremely useful in order to provide accurate information on the realistic success rate of oocyte freezing when counseling breast cancer patients who wish to have their oocytes frozen for successful pregnancy in the future. Another important issue about gamete freezing is the risk of congenital anomalies in the offspring. To date, no apparent increase in the rate of congenital anomalies has been reported as compared to US national statistics for natural conceptions reported by the US Centers for Disease Control (CDC) [124]. As there is clear evidence that overall success rates of oocyte cryopreservation are comparable to those of embryo cryopreservation, the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology finally announced that oocyte cryopreservation should no longer be considered experimental [119]. The fact that the ASRM removed the "experimental" label from oocyte cryopreservation will facilitate broader use of oocyte cryopreservation and reinforce the value of this strategy for fertility preservation in cancer patients. Indeed, clinical applications of oocyte cryopreservation would be expanded beyond fertility preservation in young cancer patients in the future.

Most human oocytes have been cryopreserved at the metaphase II stage either by slow freezing or vitrification techniques. However, controlled ovarian stimulation (COS) and egg retrieval for mature oocyte cryopreservation cannot be an option for some women, especially those with fast-growing breast cancer requiring immediate neoadjuvant chemotherapy or who are uncomfortable with elevated hormone levels during COS. In that case, cryopreservation of immature oocytes at the stage of germinal vesicle (GV) can be an attractive alternative to cryopreservation of mature oocytes, as it does not require COS and thus no delay in cancer treatment and no elevation of estrogen levels. To date, cryopreservation of immature oocytes at the GV stage has not been very successful. It appears that GV oocytes are as vulnerable to cryo-injury as mature oocytes and easily compromised for normal maturation and fertilization capacity. The possible changes after GV oocyte cryopreservation include premature chromosomal condensation, externalization of chromatin fragments into the cytoplasm, perturbations in the organization and distribution of microtubules and mitochondria, and alteration in protein synthesis activity in the cytoplasm during maturation [129]. As cryopreservation of GV oocytes is not a realistic option at present, an alternative strategy is in vitro maturation (IVM) of GV stage oocytes to MII oocytes followed by vitrification of mature oocytes. In this way, oocyte retrieval can be done without COS, and oocytes can be cryopreserved at the MII stage rather than the GV stage. The success rates with this strategy will mainly rely on the quality of IVM technology though. The role of IVM as a fertility-preserving strategy in breast cancer patients will be discussed later in more detail.

The overall divorce rate does not appear to be increased in cancer patients. But there is a gender disparity in the occurrence of divorce. An interesting study examining the role gender played in so-called partner abandonment revealed that a woman is sixs times more likely to be separated or

divorced soon after a diagnosis of cancer than if a man is the patient (20.8% vs. 2.9%) [130]. Other studies conducted in cancer survivors obtained similar results [131]. This fact underscores the importance of unfertilized gamete banking in female cancer patients facing a higher risk of divorce or separation. In such cases perhaps oocyte cryopreservation should be considered instead of embryo cryopreservation; or at least a half of the total number of oocytes should be frozen without insemination with sperm of the husband or partner.

Ovarian Tissue Cryopreservation

Ovarian cryopreservation is the only option of fertility preservation in patients in whom cancer therapy cannot be delayed because of a rapidly growing tumor; or ovarian stimulation is contraindicated for embryo or oocyte freezing. Ovarian tissue cryopreservation does not require ovarian stimulation and ovarian tissue can be harvested laparoscopically without any preparation [132]. Removed tissue is processed into thin cortical slices and frozen via slow freezing. This procedure is much less successful than embryo and oocyte cryopreservation in terms of live birth rate. Ovarian tissue cryopreservation has become a clinically feasible technology for fertility preservation in cancer patients since the report of the first live birth in 2004 and more than 50 live births reported to date after orthotopic autotransplantation of frozen-thawed human ovarian tissue in 2004 [133, 134]. To date, this strategy is the only fertility preservation option for prepubertal girls. The ovarian cortex contains primordial follicles with oocytes arrested in the diplotene of prophase of the first meiotic division. It has been suggested that the relatively high surface/volume ratio, low metabolic rate, and the absence of zona pellucida make primordial follicles less susceptible to damage from freezing [1]. Banking of ovarian tissue relies upon this feature of primordial follicles. Most ovarian tissue has been cryopreserved using slow freezing techniques, which have been successful although not optimized. Recently, vitrification of ovarian tissue has been attempted with good results [135, 136].

The age of the patient is a crucial factor to consider as the chance of restoration of ovarian function and fertility is closely correlated to the number of follicles in the ovarian graft. Only young GIS cancer patients with good ovarian reserves can be candidates for ovarian tissue freezing since more than half of the eggs in the ovary are lost during the ischemic period after grafting until re-vascularization occurs. An additional 10–15% of the oocytes will be lost during the freezing and thawing process. Current experience with human ovarian transplantation suggests that women over 38 may not be good candidates for ovarian tissue banking as the chance of pregnancy with ovarian transplantation is extremely low [116]. In addition, it is recommended to evaluate the ovarian reserve with anti-Müllerian hormone and antral follicle count (AFC) before cryopreservation of ovarian tissue.

When the patient is ready to have a family, stored ovarian tissue is thawed and transplanted either to the orthotopic or heterotopic site. In the orthotopic transplantation technique, frozen-thawed ovarian cortical pieces can be grafted near the infundibulopelvic ligament (if both ovaries were removed before) or on the existing nonfunctional ovary. In the heterotopic transplantation method, ovarian tissue can be grafted at any place other than the original site of the ovary, such as subcutaneous tissue of the forearm or rectus muscle of the abdomen. The advantage of orthotopic transplantation is that natural conception is possible. However, this technique requires an invasive procedure with general anesthesia. Heterotopic transplantation can be done without general anesthesia. It is easy to monitor follicle development, and to remove the grafts if needed. To date, orthotopic autotransplantation of frozen-thawed ovarian tissue has resulted in 24 live births worldwide [137]. On the other hand, no baby has been born after heterotopic transplantation [138]. The causes of failed conception after heterotopic ovarian transplantation can be multifactorial. One factor may be the suboptimal environment of the heterotopic site that may affect follicular development and the quality of oocytes. Indeed, environmental factors at the heterotopic site are not identical to those of the orthotopic site in the pelvis. Whereas the environment of graft sites can influence the survival of grafted ovarian tissue, the major damage to follicles is done by cryoinjury during freezing and thawing and ischemia after transplantation. The significant concern with autologous ovarian transplantation in cancer patients is the safety of transplanting stored ovarian tissue, since the risk of reintroduction of cancer cells exists in certain cancers such as leukemias. Metastases were repeatedly detected in ovarian tissue obtained for cryopreservation purposes from patients with leukemia, as well as in one patient with Ewing sarcoma. No metastases were detected in ovarian tissue from lymphoma and breast cancer patients who had their ovarian tissue cryopreserved. There are reports of ovarian tissue cryopreservation in patients with anal cancers but no information was provided regarding the analysis of the grafts for the presence of malignant cells [139]. Data is scarce on histological examination of ovarian tissue from patients with colon and gastric cancers undergoing ovarian tissue cryopreservation. But there are some clinical and autopsy studies that have indicated ovarian metastases to be present in colon and gastric carcinoma patients [140]. Therefore, there is concern about auto-transplantation safety in patients with colorectal and gastric cancers. Where safety of ovarian tissue transplantation in cancer patients is uncertain, we may need to develop and perfect new technologies including in vitro growth and maturation of follicles and/or isolated follicle transplantation instead of autotransplantation.

Gonadotropin-Releasing Hormone (GnRH) Analogs

The administration of gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy has been proposed as a potential fertility-preservation strategy to preserve ovarian reserve after emergence of the promising findings from anecdotal reports, primate models, and non-randomized trials in humans [141]. However, randomized controlled trials (RCTs) have shown inconsistent results in female patients with cancer, giving rise to a debate among the physicians and scientists in the fields of oncology and reproductive medicine over the actual role of GnRHa in the prevention of chemotherapy-induced ovarian failure. Some of these trials demonstrated a protective effect of GnRHa in preserving ovarian function after chemotherapy [142–145], whereas other trials did not [146–148]. The professional societies of oncology and reproductive medicine/fertility preservation currently emphasize lack of a proven molecular mechanism with gonadal protection with GnRHa during chemotherapy, and underscore the need for research in this understudied issue [116, 141]. Various mechanisms have been suggested, including GnRHa-induced decrease in the number of primordial follicles entering the differentiation stage, reduction of ovarian perfusion due to a GnRHa-induced hypoestrogenic state, and decreased ovarian cell apoptosis, through either activation of GnRH receptors or upregulation of intragonadal antiapoptotic molecules (GnRHas) during adjuvant chemotherapy. But none of these theories has been validated so far [88, 141, 149]. We have recently shown that GnRH agonist leuprolide acetate neither activated antiapoptotic pathways nor conferred any protection against chemotherapy-induced follicle death in human ovary in vitro [150]. Because of no clear protective effects of GnRHa, GnRHa should not be offered among the first-line fertility preservation methods, but can be considered as a backup method in cancer patients.

In Vitro Maturation of Oocytes (IVM)

Vitrification of mature oocytes harvested after controlled ovarian simulation has recently become an established method to preserve fertility of cancer patients as mentioned previously. But mature oocytes cannot be obtained if there is no sufficient time for ovarian stimulation; or there is a contraindication for it. In these cases, immature oocytes can be retrieved without ovarian stimulation in both follicular and luteal phases before exposure to gonadotoxic therapies for breast cancer patients. This also avoids exposure to supraphysiological levels of estrogens. Immature oocytes can also be collected from antral follicles during ovarian cryopreservation, and both procedures can be combined [151]. Germinal vesicle (GV) stage and metaphase-I (MI) oocytes are immature ones that can be matured into metaphase II (MII) oocytes using special in vitro maturation solutions. GV and MI oocytes can be frozen but their maturational capacity after warming is lower than fresh ones [152]. Therefore, they have to be matured to MII stage before cryopreservation. Mature oocytes can be frozen; or fertilized and preserved as embryos. In a retrospective cohort analysis of 66 patients with breast cancer, immature oocytes were collected and matured in vitro and then either vitrified (group 1, $n = 35$) or fertilized and preserved as vitrified embryos (group 2, $n = 31$). In group 1 the average number of oocytes retrieved was 11.4 ± 8.8, the maturation rate was 64.2%, and an average of 7.9 ± 6.6 oocytes were vitrified per patient treated. In group 2 (vitrified embryos) the average number of oocytes retrieved was 9.7 ± 6.4, the maturation rate was 53.2%, and an average of 5.8 ± 2.7 mature oocytes were available for fertilization per patient. The fertilization rate was 77.8%, resulting in 4.5 ± 2.7 vitrified embryos per patient. Calculated pregnancy rates per vitrified oocyte and embryo were 3.8% and 8.1%, respectively [153]. In summary, IVM combined with oocyte or embryo freezing can be a viable option for some breast cancer patients since it avoids the delay of cancer treatment and possible exposure to the supraphysiological level of estrogen. However, the technique itself requires more expertise and experience compared to the standard IVF procedure.

Ovarian Transposition

Transposing the ovaries out of the radiation field is an option for preserving gonadal function. Females treated with whole abdominal and/or pelvic irradiation for Hodgkin disease, Wilms tumor, or other solid tumors, or colorectal tumors (e.g., rhabdomyosarcoma, neuroblastoma) are at high risk of AOF [154]. If no chemotherapy is planned that would result in definite gonadal failure, the ovaries can be surgically moved with their vascular pedicle outside the pelvis (transposed) to shield them from radiation therapy. When ovarian transposition is performed prior to radiotherapy, ovarian function is retained in the majority of young girls and adolescent females [155, 156]. Spontaneous pregnancies and live births have been reported after transposition of the ovaries [157]. If the patient is to undergo an abdominal surgery, the ovaries can be transposed at the same time. Laparoscopic surgery to mobilize the ovaries is easily performed on an outpatient basis with minimal risk to the patient before the scheduled radiotherapy. Small metal clips are often placed on the ovary to outline its new position so the radiation oncologist may identify the ovary prior to initiating treatment. The success retaining ovarian function with ovarian transposition prior to radiotherapy varies between 16% and 90% [154]. Success rates are affected by the degree of scatter radiation, vascular compromise, the age of the patient, dose of radiation, whether the ovaries were shielded, and whether concomitant chemotherapy is used [154]. Fallopian tube infarction, chronic ovarian pain, ovarian cyst formation, and

migration of ovaries back to their original position before radiotherapy is completed are reported complications [158]. Patients undergoing pelvic radiation must be made aware of the fact that ovarian transposition will not circumvent the harmful effects of radiation on the uterus and other pelvic structures, which might prevent them from carrying a pregnancy.

Males

Male patient with GI cancers should be considered for preserving fertility before treatment. In a survey conducted among 201 young male cancer survivors, it was found that only 51% of the patients were offered sperm banking prior to cancer treatment [4]. Impairment of spermatogenesis can exist before, during, or after cancer treatment, and it was shown that stress caused by the psychological effects of cancer diagnosis might have a negative impact on spermatogenesis [159]. It is impossible to predict who will be affected permanently, but initial assessment should be done with:

1. Semen analysis (World Health Organization criteria [160])— volume 1.5 (1.4–1.7) ml, sperm concentration 15 (12–16) million/ml, progressive motility 32 (31–34%), and vitality 58 (55–63%)
2. Hormonal analysis—FSH, LH, and testosterone

The most reliable and extensively used method for adult male fertility preservation is sperm cryopreservation (Fig. 35.2). Besides ejaculated semen, testicular sperm extraction from testicular biopsies might be an option for sperm retrieval in azoospermic male patients and boys unable to ejaculate. Assisted ejaculation techniques (i.e., penile vibratory stimulation and electroejaculation) can be used in patients who are not capable of ejaculation via masturbation due to their physical and psychological state [9, 161]. Although sperm banking is well established in adult fertility preservation, it still remains a challenge in adolescents and prepubertal boys. The other techniques that can be utilized in male fertility preservation include cryopreservation of testicular tissue or spermatogonial stem cell (SSC), testicular xenografting, in vitro germ cell maturation, and artificial gametes, which are mostly experimental [9, 162].

Sperm Cryopreservation (Banking)

Sperm cryopreservation is the most reliable choice of method to preserve male fertility before cancer treatment [159]. It has been described in the eighteenth century and became feasible with the development of sperm cryoprotectants in the mid-1900s [163]. Collecting semen samples via masturbation is the preferred method because it allows obtaining high-quality sperm with the lowest cost. Using lubricants must be avoided as these materials are often toxic to sperm [164].

An alpha agonist may be useful to direct ejaculate forward in patients with a history of retrograde ejaculation history.

In azoospermic males, surgical sperm extraction techniques such as microsurgical testicular sperm extraction (mTESE) and microsurgical epididymal sperm aspiration (MESA) can be the method of choice [164].

If the male patient is too ill to collect sample by ejaculation, electroejaculation, percutaneous epididymal sperm aspiration, or needle testicular sperm extraction (TESE) or testicular sperm aspiration (TESA) options are available techniques.

Testicular Tissue Cryopreservation This is an investigational technique for fertility preservation that is used for prepubertal boys. This technology is experimental and it

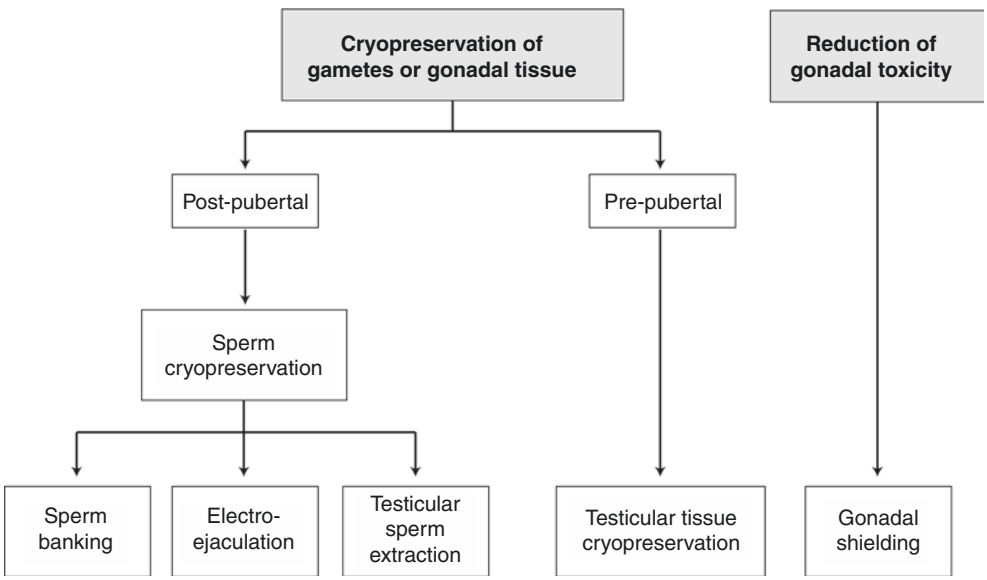


Fig. 35.2 Some methods to preserve adult male fertility

should be remembered that it has not been demonstrated successfully in humans [165–167].

Gonadal Shielding For males receiving radiation therapy only, gonadal shielding may be an option if sperm collection is not possible [168, 169]. Suppression of testicular function during chemotherapy by the administration of gonadotropin-releasing hormone (GnRH) agonists has not been successful and is not recommended as the main protective.

Conclusion

Practice behavior of physicians in referring cancer patients for fertility preservations is another relatively understudied issue. Unfortunately, a considerable number of patients feel that their cancer physicians do not sufficiently inform them about the impact of the cancer therapy on fertility and the options to preserve it (Figs. 35.3a, b and 35.4 [48]). Even though some oncologists appear to discuss routinely a treatment's impact on fertility, few indeed refer their patients to reproductive endocrinologists. When planning treatment, 30% rarely consider a woman's desire for fertility. Gynecologic oncologists were more likely to routinely consider fertility compared with other oncologists (93% vs. 60%). Gynecologic oncologists also were more likely to provide a less effective regimen to better preserve fertility (61% vs. 37%). Most oncologists (86%) would be willing to sacrifice less than a 5% reduction in disease-free survival if a regimen offered better fertility outcomes; 36% felt patients would be willing to sacrifice >5% [118]. Another survey that examined oncologists' referral practice patterns for fertility preservation among US physicians using the American Medical

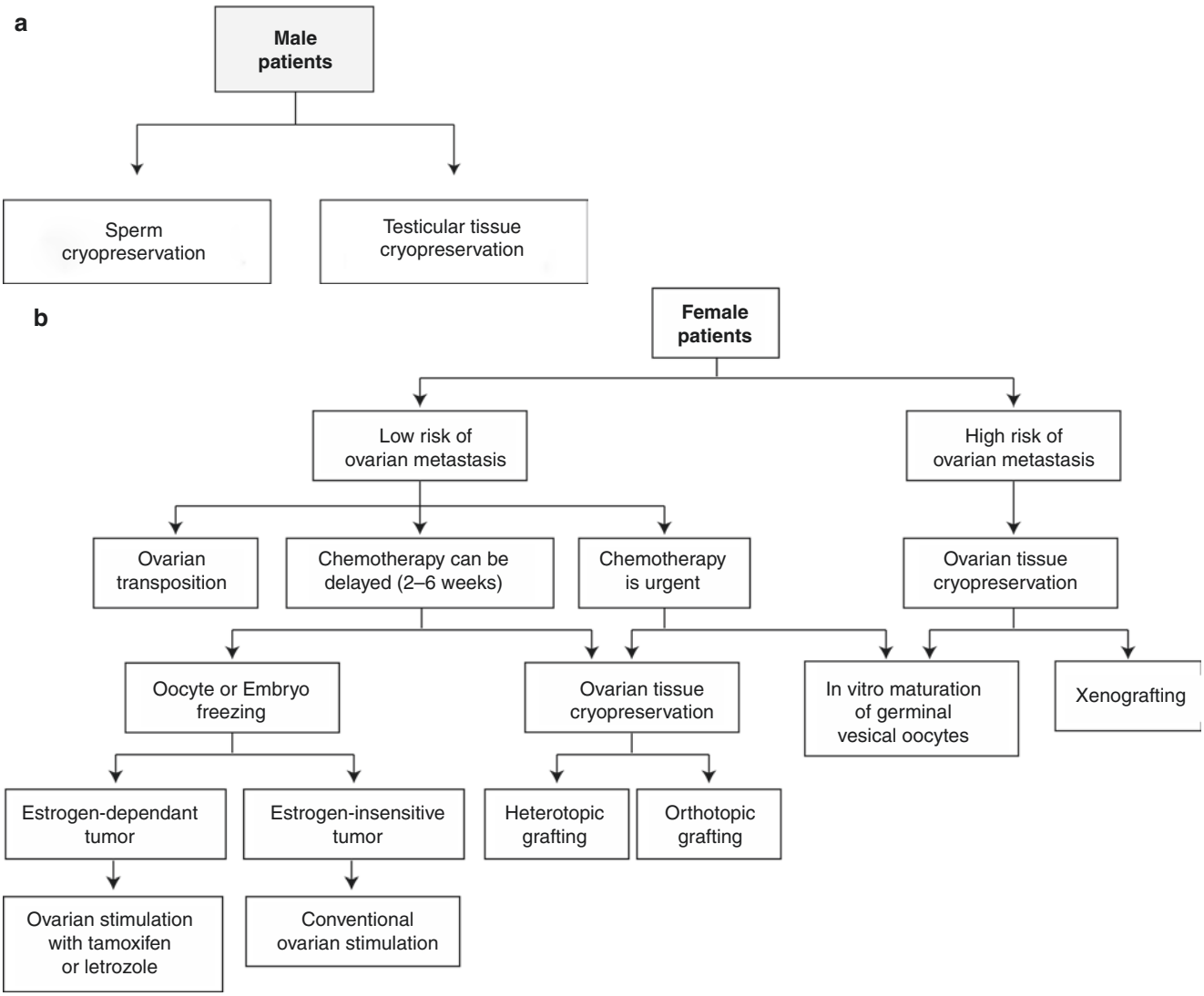


Fig. 35.3 National Comprehensive Cancer Network (NCCN) recommendations: (**a**) male, (**b**) female

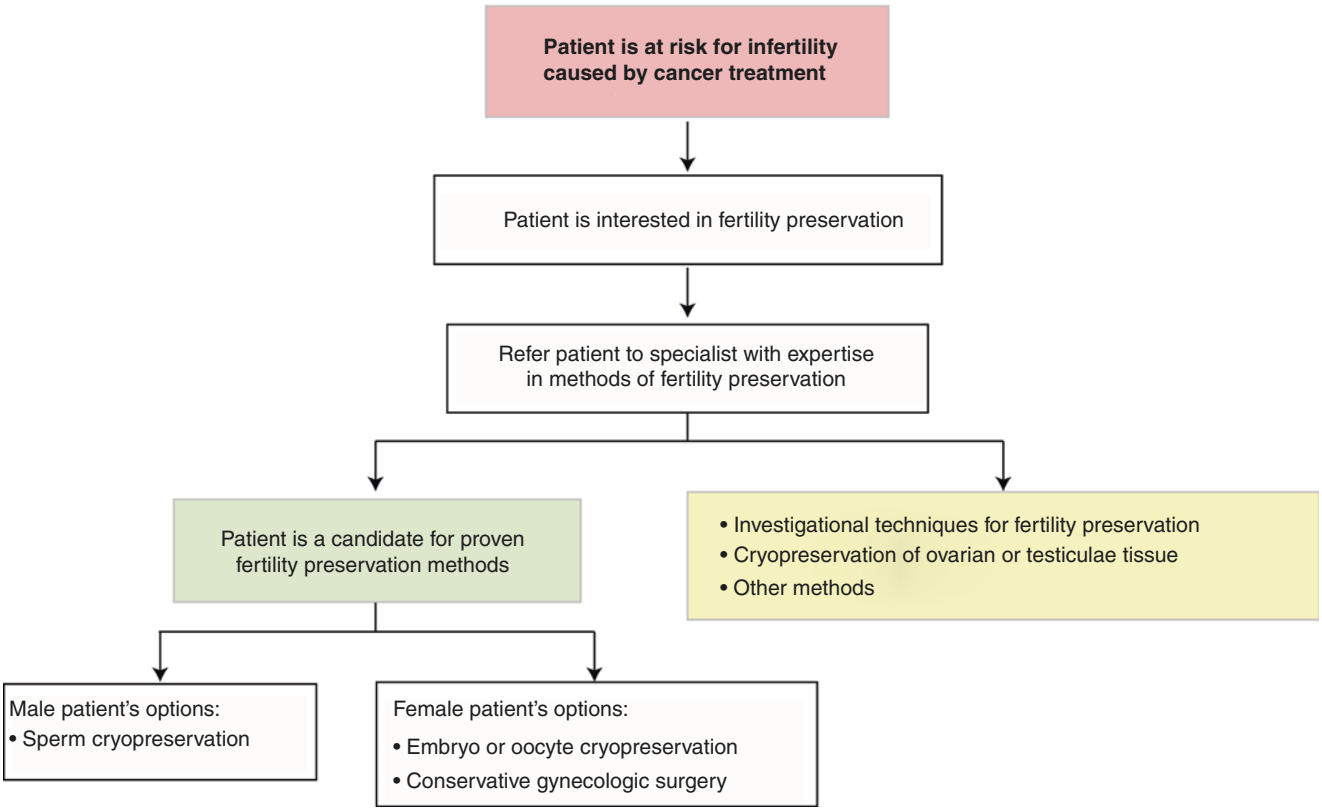


Fig. 35.4 American Society of Clinical Oncology (ASCO) 2013 recommendations. (Adapted from [48])

Association Physician Masterfile database demonstrated that referrals were more likely among female physicians and that less than half of US physicians are following the guidelines from the American Society of Clinical Oncology, which suggest that all patients of childbearing age should be informed about fertility preservation. These results not only show us that fertility preservation is still not well perceived among physicians but also underscore the critical role of oncologists at academic medical centers in informing and referring cancer patients who have concerns about their fertility.

References

1. Oktem O, Urman B. Options of fertility preservation in female cancer patients. Obstet Gynecol Surv. 2010;65(8):531–42.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
3. Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer. A pilot survey of survivors' attitudes and experiences. Cancer. 1999;86(4):697–709.
4. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. J Clin Oncol. 2002;20(7):1880–9.
5. Kumar A, Merali A, Pond GR, Zbuk K. Fertility risk discussions in young patients diagnosed with colorectal cancer. Curr Oncol. 2012;19(3):155–9.
6. Oktem O, Oktay K. The ovary: Anatomy and function throughout human life. Ann N Y Acad Sci. 2008;1127:1–9.
7. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol. 1996;14(5):1718–29.
8. Puscheck E, Philip PA, Jeyendran RS. Male fertility preservation and cancer treatment. Cancer Treat Rev. 2004;30(2):173–80.
9. Livne-Segev D, Forbes EC, Lo KC. State-of-the art advances in fertility preservation for the male cancer patient. Future Oncol. 2016;12(14):1691–4.
10. Rivkees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA. 1988;259(14):2123–5.
11. Costabile RA. The effects of cancer and cancer therapy on male reproductive function. J Urol. 1993;149(5 Pt 2):1327–30.
12. Roeser HP, Stocks AE, Smith AJ. Testicular damage due to cytotoxic drugs and recovery after cessation of therapy. Aust NZ J Med. 1978;8(3):250–4.
13. Meistrich ML, Chawla SP, Da Cunha MF, Johnson SL, Plager C, Papadopoulos NE, et al. Recovery of sperm production after chemotherapy for osteosarcoma. Cancer. 1989;63(11):2115–23.
14. Averette HE, Boike GM, Jarrell MA. Effects of cancer chemotherapy on gonadal function and reproductive capacity. CA Cancer J Clin. 1990;40(4):199–209.
15. Pryzant RM, Meistrich ML, Wilson G, Brown B, McLaughlin P. Long-term reduction in sperm count after chemotherapy with and without radiation therapy for non-hodgkin's lymphomas. J Clin Oncol. 1993;11(2):239–47.
16. Brydoy M, Fossa SD, Klepp O, Bremnes RM, Wist EA, Wentzel-Larsen T, et al. Paternity following treatment for testicular cancer. J Natl Cancer Inst. 2005;97(21):1580–8.

17. Schilsky RL, Lewis BJ, Sherins RJ, Young RC. Gonadal dysfunction in patients receiving chemotherapy for cancer. Ann Intern Med. 1980;93(1):109–14.
18. Pont J, Albrecht W. Fertility after chemotherapy for testicular germ cell cancer. Fertil Steril. 1997;68(1):1–5.
19. Fairley KF, Barrie JU, Johnson W. Sterility and testicular atrophy related to cyclophosphamide therapy. Lancet. 1972;1(7750):568–9.
20. Meistrich ML. Relationship between spermatogonial stem cell survival and testis function after cytotoxic therapy. Br J Cancer Suppl. 1986;7:89–101.
21. Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin N Am. 1998;27(4):927–43.
22. Howell SJ, Radford JA, Ryder WD, Shalet SM. Testicular function after cytotoxic chemotherapy: evidence of leydig cell insufficiency. J Clin Oncol. 1999;17(5):1493–8.
23. Howell SJ, Radford JA, Adams JE, Smets EM, Warburton R, Shalet SM. Randomized placebo-controlled trial of testosterone replacement in men with mild leydig cell insufficiency following cytotoxic chemotherapy. Clin Endocrinol. 2001;55(3):315–24.
24. Shamberger RC, Rosenberg SA, Seipp CA, Sherins RJ. Effects of high-dose methotrexate and vincristine on ovarian and testicular functions in patients undergoing postoperative adjuvant treatment of osteosarcoma. Cancer Treat Rep. 1981;65(9–10):739–46.
25. Choo YC, Chan SY, Wong LC, Ma HK. Ovarian dysfunction in patients with gestational trophoblastic neoplasia treated with short intensive courses of etoposide (vp-16-213). Cancer. 1985;55(10):2348–52.
26. Matsui H, Eguchi O, Kimura H, Inaba N, Takamizawa H. the effect of etoposide on ovarian function in patients with gestational trophoblastic disease. Nippon Sanka Fujinka Gakkai Zasshi. 1993;45(5):437–43.
27. Matsui H, Seki K, Sekiya S, Takamizawa H. Reproductive status in gtd treated with etoposide. J Reprod Med. 1997;42(2):104–10.
28. Plowchalk DR, Mattison DR. Phosphoramide mustard is responsible for the ovarian toxicity of cyclophosphamide. Toxicol Appl Pharmacol. 1991;107(3):472–81.
29. Gill S, Blackstock AW, Goldberg RM. Colorectal cancer. Mayo Clin Proc. 2007;82(1):114–29.
30. Maindrault-Goebel F, Louvet C, Andre T, Carola E, Lotz JP, Molitor JL, et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (folfox6). Gercor. Eur J Cancer. 1999;35(9):1338–42.
31. Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the bicc-c study. J Clin Oncol. 2007;25(30):4779–86.
32. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-folfox4 treatment and ras mutations in colorectal cancer. N Engl J Med. 2013;369(11):1023–34.
33. Cercek A, Siegel CL, Capanu M, Reidy-Lagunes D, Saltz LB. Incidence of chemotherapy-induced amenorrhea in premenopausal women treated with adjuvant folfox for colorectal cancer. Clin Colorectal Cancer. 2013;12(3):163–7.
34. Wan J, Gai Y, Li G, Tao Z, Zhang Z. Incidence of chemotherapy- and chemoradiotherapy-induced amenorrhea in premenopausal women with stage ii/iii colorectal cancer. Clin Colorectal Cancer. 2015;14(1):31–4.
35. Utsunomiya T, Tanaka T, Utsunomiya H, Umesaki N. A novel molecular mechanism for anticancer drug-induced ovarian failure: irinotecan hcl, an anticancer topoisomerase i inhibitor, induces specific fasl expression in granulosa cells of large ovarian follicles to enhance follicular apoptosis. Int J Oncol. 2008;32(5):991–1000.
36. Tanaka T, Utsunomiya T, Utsunomiya H, Umesaki N. Irinotecan hcl, an anticancer topoisomerase i inhibitor, frequently induces ovarian failure in premenopausal and perimenopausal women. Oncol Rep. 2008;19(5):1123–33.
37. Jou E, Rajdev L. Current and emerging therapies in unresectable and recurrent gastric cancer. World J Gastroenterol. 2016;22(20):4812–23.
38. Berliere M, Dalenc F, Malingret N, Vindevogel A, Piette P, Roche H, et al. Incidence of reversible amenorrhea in women with breast cancer undergoing adjuvant anthracycline-based chemotherapy with or without docetaxel. BMC Cancer. 2008;8:56.
39. Nabholtz J, Pienkowski T, Mackey J. Phase iii trial comparing tac (docetaxel, doxorubicin, cyclophosphamide) with fac (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (bc) patients: interim analysis of the bcirg 001 study. Proc Annu Meet Am Soc Clin Oncol. 2002;141. (Abstract).
40. Hortobagyi GN, Buzdar AU, Marcus CE, Smith TL. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at m.D. Anderson hospital and tumor institute. NCI Monogr. 1986;1:105–9.
41. NSABP C-08 Study. https://www.gene.com/download/pdf/Avastin_dear_HCP_Letter.pdf. Accessed on 12 May 2019.
42. Zamah AM, Mauro MJ, Druker BJ, Oktay K, Egorin MJ, Cedars MI, et al. Will imatinib compromise reproductive capacity? Oncologist. 2011;16(10):1422–7.
43. Christopoulos C, Dimakopoulou V, Rotas E. Primary ovarian insufficiency associated with imatinib therapy. N Engl J Med. 2008;358(10):1079–80.
44. Gonfloni S, Di Tella L, Caldarola S, Cannata SM, Klinger FG, Di Bartolomeo C, et al. Inhibition of the c-abl-tap63 pathway protects mouse oocytes from chemotherapy-induced death. Nat Med. 2009;15(10):1179–85.
45. Kerr JB, Hutt KJ, Cook M, Speed TP, Strasser A, Findlay JK, et al. Cisplatin-induced primordial follicle oocyte killing and loss of fertility are not prevented by imatinib. Nat Med. 2012;18(8):1170–2; author reply 1172–1174.
46. Bildik G, Akin N, Urman B, Oktem O. Imatinib mesylate accelerates follicle death and is not protective against chemotherapy induced damage in human ovary. Hum Reprod. 2016;31(Suppl 1):e81.
47. Chapman RM. Effect of cytotoxic therapy on sexuality and gonadal function. Semin Oncol. 1982;9(1):84–94.
48. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American society of clinical oncology clinical practice guideline update. J Clin Oncol. 2013;31(19):2500–10.
49. Schrader M, Muller M, Straub B, Miller K. The impact of chemotherapy on male fertility: a survey of the biologic basis and clinical aspects. Reprod Toxicol. 2001;15(6):611–7.
50. Meistrich ML, Wilson G, Brown BW, da Cunha MF, Lipshultz LI. Impact of cyclophosphamide on long-term reduction in sperm count in men treated with combination chemotherapy for ewing and soft tissue sarcomas. Cancer. 1992;70(11):2703–12.
51. Bordallo MA, Guimaraes MM, Pessoa CH, Carrico MK, Dimetz T, Gazolla HM, et al. Decreased serum inhibin b/fsh ratio as a marker of sertoli cell function in male survivors after chemotherapy in childhood and adolescence. J Pediatr Endocrinol Metab. 2004;17(6):879–87.
52. Devita VT Jr, Lawrence TS, Rosenberg SA, editors. Cancer: principles & practice of oncology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
53. Levi M, Shalgi R, Brenner B, Perl G, Purim O, Amit L, et al. The impact of oxaliplatin on the gonads: from bedside to the bench. Mol Hum Reprod. 2015;21(12):885–93.
54. D'Souza UJ. Toxic effects of 5-fluorouracil on sperm count in wistar rats. Malays J Med Sci. 2003;10(1):43–5.

55. Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of sn-38, a metabolite of the camptothecin derivative cpt-11, in the antitumor effect of cpt-11. Cancer Res. 1991;51(16):4187–91.
56. Lopes F, Smith R, Nash S, Mitchell RT, Spears N. Irinotecan metabolite sn38 results in germ cell loss in the testis but not in the ovary of prepubertal mice. Mol Hum Reprod. 2016;22(11):745–55.
57. UK CR. [February 13, 2018]; Available from: www.cancerresearchuk.org.
58. Aass N, Fossa SD, Theodorsen L, Norman N. Prediction of long-term gonadal toxicity after standard treatment for testicular cancer. Eur J Cancer. 1991;27(9):1087–91.
59. Petersen PM, Hansen SW, Giwercman A, Rorth M, Skakkebaek NE. Dose-dependent impairment of testicular function in patients treated with cisplatin-based chemotherapy for germ cell cancer. Ann Oncol. 1994;5(4):355–8.
60. Petersen PM, Skakkebaek NE, Giwercman A. Gonadal function in men with testicular cancer: Biological and clinical aspects. APMIS. 1998;106(1):24–34; discussion 34–26.
61. Viveka S, Udyavar A, Shetty B, Kuriakose S, Sudha MJ. Histomorphometric effects of gemcitabine on swiss albino mice spermatogenesis. Adv Biomed Res. 2015;4:29.
62. Levi M, Popovtzer A, Tzabari M, Mizrachi A, Savion N, Stemmer SM, et al. Cetuximab intensifies cisplatin-induced testicular toxicity. Reprod Biomed Online. 2016;33(1):102–10.
63. Anonymous. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet. 2001;358(9290):1291–304.
64. Glimelius B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol. 2003;42(5–6):476–92.
65. Anonymous. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish rectal cancer trial. N Engl J Med. 1997;336(14):980–7.
66. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638–46.
67. Cedermark B, Johansson H, Rutqvist LE, Wilking N. The stockholm i trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm colorectal cancer study group. Cancer. 1995;75(9):2269–75.
68. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B. The stockholm ii trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer. 2001;92(4):896–902.
69. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol. 2005;23(24):5644–50.
70. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The tme trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007;246(5):693–701.
71. Marijnen CA, Nagtegaal ID, Kapiteijn E, Kranenbarg EK, Noordijk EM, van Krieken JH, et al. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. Int J Radiat Oncol Biol Phys. 2003;55(5):1311–20.
72. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (mrc cr07 and ncic-ctg c016): a multicentre, randomised trial. Lancet. 2009;373(9666):811–20.
73. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. Dis Colon Rectum. 1993;36(6):564–72.
74. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40.
75. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. Conventionally fractionated radiochemotherapy. Radiother Oncol. 2004;72(1):15–24.
76. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93(10):1215–23.
77. Pietrzak L, Bujko K, Nowacki MP, Kepka L, Oledzki J, Rutkowski A, et al. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial. Radiother Oncol. 2007;84(3):217–25.
78. Bujko K, Nowacki MP, Kepka L, Oledzki J, Bebenek M, Kryj M. Postoperative complications in patients irradiated preoperatively for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs chemoradiation. Color Dis. 2005;7(4):410–6.
79. Ngan SY, Fisher R, Goldstein D, Solomon M, Burmeister BH, Ackland SP, et al. A randomized trial comparing local recurrence (lr) rates between short-course (sc) and long-course (lc) preoperative radiotherapy (rt) for clinical t3 rectal cancer: An intergroup trial (trog, agitg, cssanz, racs). J Clin Oncol. 2010;28:15s.. (suppl; abstr 3509).
80. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Krynski J, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5× 5 gy and consolidation chemotherapy for ct4 or fixed ct3 rectal cancer: Results of a randomized phase iii study. Ann Oncol. 2016;27(5):834–42.
81. Nilsson PJ, van Etten B, Hospers GA, Pahlman L, van de Velde CJ, Beets-Tan RG, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer–the rapido trial. BMC Cancer. 2013;13:279.
82. Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in mri-defined poor-risk rectal cancer: A phase 2 trial. Lancet Oncol. 2010;11(3):241–8.
83. Fernandez-Martos C, Pericay C, Aparicio J, Salud A, Safont M, Massuti B, et al. Phase ii, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (capox) compared with induction capox followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: grupo cancer de recto 3 study. J Clin Oncol. 2010;28(5):859–65.
84. Fernandez-Martos C, Garcia-Albeniz X, Pericay C, Maurel J, Aparicio J, Montagut C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the spanish gcr-3 phase ii randomized trialdagger. Annals of Oncology. 2015;26(8):1722–8.
85. Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Cancer Netw. 2014;12(4):513–9.

86. Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Effect of adding mfolfox6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015;16(8):957–66.
87. George TJ, Yothers G, Hong TS, Russell MM, You YN, Parker W, et al. Nrg-gi002: a phase ii clinical trial platform for total neoadjuvant therapy (tnt) in rectal cancer. J Clin Oncol. 2017;35(15_suppl):TPS3629-TPS3629.
88. Oktem O, Oktay K. A novel ovarian xenografting model to characterize the impact of chemotherapy agents on human primordial follicle reserve. Cancer Res. 2007;67(21):10159–62.
89. Oktem O, Oktay K. Preservation of menstrual function in adolescent and young females. Ann N Y Acad Sci. 2008;1135:237–43.
90. Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. Hum Reprod. 2003;18(1):117–21.
91. Adriaens I, Smitz J, Jacquet P. The current knowledge on radiosensitivity of ovarian follicle development stages. Hum Reprod Update. 2009;15(3):359–77.
92. Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. J Natl Cancer Inst Monogr. 2005;34:64–8.
93. Sudour H, Chastagner P, Claude L, Desandes E, Klein M, Carrie C, et al. Fertility and pregnancy outcome after abdominal irradiation that included or excluded the pelvis in childhood tumor survivors. Int J Radiat Oncol Biol Phys. 2010;76(3):867–73.
94. Beneventi F, Locatelli E, Giorgiani G, Zecca M, Locatelli F, Cavagnoli C, et al. Gonadal and uterine function in female survivors treated by chemotherapy, radiotherapy, and/or bone marrow transplantation for childhood malignant and non-malignant diseases. BJOG. 2014;121(7):856–65.. discussion 865
95. Bruheim K, Svartberg J, Carlsen E, Dueland S, Haug E, Skovlund E, et al. Radiotherapy for rectal cancer is associated with reduced serum testosterone and increased fsh and lh. Int J Radiat Oncol Biol Phys. 2008;70(3):722–7.
96. Budgell GJ, Cowan RA, Hounsell AR. Prediction of scattered dose to the testes in abdominopelvic radiotherapy. Clin Oncol (R Coll Radiol). 2001;13(2):120–5.
97. Colpi GM, Contalbi GF, Nerva F, Sagone P, Piediferro G. Testicular function following chemo-radiotherapy. Eur J Obstet Gynecol Reprod Biol. 2004;113(Suppl 1):S2–6.
98. Piroth MD, Hensley F, Wannenmacher M, Zierhut D. Male gonadal dose in adjuvant 3-d-pelvic irradiation after anterior resection of rectal cancer. Influence to fertility. Strahlenther Onkol. 2003;179(11):754–9.
99. Bakkal BH, Vural T, Elmas O, Yildiz O, Kokturk F. Effect of treatment position and radiotherapy planning on testicular dose in patients with rectal carcinoma. J Cancer Res Ther. 2014;10(3):558–62.
100. Hermann RM, Henkel K, Christiansen H, Vorwerk H, Hille A, Hess CF, et al. Testicular dose and hormonal changes after radiotherapy of rectal cancer. Radiother Oncol. 2005;75(1):83–8.
101. Mazonakis M, Damilakis J, Varveris H, Gourtsouiannis N. Radiation dose to testes and risk of infertility from radiotherapy for rectal cancer. Oncol Rep. 2006;15(3):729–33.
102. Buchli C, Al Abani M, Ahlberg M, Holm T, Fokstuen T, Bottai M, et al. Assessment of testicular dose during preoperative radiotherapy for rectal cancer. Acta Oncol. 2016;55(4):496–501.
103. Zhao J, Hu W, Cai G, Wang J, Xie J, Peng J, et al. Dosimetric comparisons of vmat, imrt and 3dcrt for locally advanced rectal cancer with simultaneous integrated boost. Oncotarget. 2016;7(5):6345–51.
104. Baglan KL, Frazier RC, Yan D, Huang RR, Martinez AA, Robertson JM. The dose-volume relationship of acute small bowel toxicity from concurrent 5-fu-based chemotherapy and radiation therapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2002;52(1):176–83.
105. Tho LM, Glegg M, Paterson J, Yap C, MacLeod A, McCabe M, et al. Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer: investigating dose-volume relationships and role for inverse planning. Int J Radiat Oncol Biol Phys. 2006;66(2):505–13.
106. Robertson JM, Lockman D, Yan D, Wallace M. The dose-volume relationship of small bowel irradiation and acute grade 3 diarrhea during chemoradiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2008;70(2):413–8.
107. Duthoy W, De Gersem W, Vergote K, Boterberg T, Derie C, Smeets P, et al. Clinical implementation of intensity-modulated arc therapy (imat) for rectal cancer. Int J Radiat Oncol Biol Phys. 2004;60(3):794–806.
108. Guerrero Urbano MT, Henrys AJ, Adams EJ, Norman AR, Bedford JL, Harrington KJ, et al. Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. Int J Radiat Oncol Biol Phys. 2006;65(3):907–16.
109. Arbea L, Ramos LI, Martinez-Monge R, Moreno M, Aristu J. Intensity-modulated radiation therapy (imrt) vs. 3d conformal radiotherapy (3dcrt) in locally advanced rectal cancer (larc): dosimetric comparison and clinical implications. Radiat Oncol. 2010;5:17.
110. Mok H, Crane CH, Palmer MB, Briere TM, Beddar S, Delclos ME, et al. Intensity modulated radiation therapy (imrt): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. Radiat Oncol. 2011;6:63.
111. Richetti A, Fogliata A, Clivio A, Nicolini G, Pesce G, Salati E, et al. Neo-adjuvant chemo-radiation of rectal cancer with volumetric modulated arc therapy: summary of technical and dosimetric features and early clinical experience. Radiat Oncol. 2010;5:14.
112. Cilla S, Caravatta L, Picardi V, Sabatino D, Macchia G, Digesu C, et al. Volumetric modulated arc therapy with simultaneous integrated boost for locally advanced rectal cancer. Clin Oncol (R Coll Radiol). 2012;24(4):261–8.
113. Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys. 2009;74(3):824–30.
114. Valentini V, Gambacorta MA, Barbaro B, Chiloiro G, Coco C, Das P, et al. International consensus guidelines on clinical target volume delineation in rectal cancer. Radiother Oncol. 2016;120(2):195–201.
115. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American society of clinical oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24(18):2917–31.
116. Kim SS, Donnez J, Barri P, Pellicer A, Patrizio P, Rosenwaks Z, et al. Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer. J Assist Reprod Genet. 2012;29(6):465–8.
117. Strong M, Peche W, Scaife C. Incidence of fertility counseling of women of child-bearing age before treatment for colorectal cancer. Am J Surg. 2007;194(6):765–7; discussion 767–768.
118. Forman EJ, Anders CK, Behera MA. Pilot survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. J Reprod Med. 2009;54(4):203–7.
119. Practice Committees of American Society for Reproductive M, Society for Assisted Reproductive T. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013;99(1):37–43.
120. De Geyter CH, Calhaz-Jorge C, Kupka MS, Wyns C, Mocanu E, Motrenko T, Scaravelli G, Smeenk J, Vidakovic S, Goossens V. The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology

(ESHRE), ART in Europe, 2014: results generated from European registries by ESHRE: The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Hum Reprod. 2018;33(9):1586–601.
121. Society of Assisted Reproductive Technology. National Summary Report 2016. 2018; Url: sart.org, Accessed on 12 May 2019.
122. Chen C. Pregnancy after human oocyte cryopreservation. Lancet. 1986;1(8486):884–6.
123. Cobo A, Diaz C. Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2011;96(2):277–85.
124. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online. 2009;18(6):769–76.
125. Cobo A, Meseguer M, Remohi J, Pellicer A. Use of cryobanked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod. 2010;25(9):2239–46.
126. Stoop D, Ermini B, Polyzos NP, Haentjens P, De Vos M, Verheyen G, et al. Reproductive potential of a metaphase ii oocyte retrieved after ovarian stimulation: an analysis of 23 354 icsi cycles. Hum Reprod. 2012;27(7):2030–5.
127. Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. Fertil Steril. 2006;86(1):70–80.
128. Rienzi L, Cobo A, Paffoni A, Scarduelli C, Capalbo A, Vajta G, et al. Consistent and predictable delivery rates after oocyte vitrification: an observational longitudinal cohort multicentric study. Hum Reprod. 2012;27(6):1606–12.
129. Van Blerkom J. Maturation at high frequency of germinal-vesicle-stage mouse oocytes after cryopreservation: alterations in cytoplasmic, nuclear, nucleolar and chromosomal structure and organization associated with vitrification. Hum Reprod. 1989;4(8):883–98.
130. Glantz MJ, Chamberlain MC, Liu Q, Hsieh CC, Edwards KR, Van Horn A, et al. Gender disparity in the rate of partner abandonment in patients with serious medical illness. Cancer. 2009;115(22):5237–42.
131. Kirchhoff AC, Yi J, Wright J, Warner EL, Smith KR. Marriage and divorce among young adult cancer survivors. J Cancer Surv. 2012;6(4):441–50.
132. Oktay K, Oktem O. Ovarian cryopreservation and transplantation for fertility preservation for medical indications: report of an ongoing experience. Fertil Steril. 2010;93(3):762–8.
133. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004;364(9443):1405–10.
134. Donnez J, Dolmans MM. Ovarian cortex transplantation: 60 reported live births brings the success and worldwide expansion of the technique towards routine clinical practice. J Assist Reprod Genet. 2015;32(8):1167–70.
135. Amorim CA, Dolmans MM, David A, Jaeger J, Vanacker J, Camboni A, et al. Vitrification and xenografting of human ovarian tissue. Fertil Steril. 2012;98(5):1291–8.. e1291–1292
136. Sheikhi M, Hultenby K, Niklasson B, Lundqvist M, Hovatta O. Clinical grade vitrification of human ovarian tissue: an ultrastructural analysis of follicles and stroma in vitrified tissue. Hum Reprod. 2011;26(3):594–603.
137. Donnez J, Dolmans MM, Pellicer A, Diaz-Garcia C, Sanchez Serrano M, Schmidt KT, et al. Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. Fertil Steril. 2013;99(6):1503–13.
138. Kim SS. Assessment of long term endocrine function after transplantation of frozen-thawed human ovarian tissue to the heterotopic site: 10 year longitudinal follow-up study. J Assist Reprod Genet. 2012;29(6):489–93.
139. Dittrich R, Mueller A, Binder H, Oppelt PG, Renner SP, Goecke T, et al. First retransplantation of cryopreserved ovarian tissue following cancer therapy in germany. Dtsch Arztebl Int. 2008;105(15):274–8.
140. Bastings L, Beerendonk CC, Westphal JR, Massuger LF, Kaal SE, van Leeuwen FE, et al. Autotransplantation of cryopreserved ovarian tissue in cancer survivors and the risk of reintroducing malignancy: a systematic review. Hum Reprod Update. 2013;19(5):483–506.
141. Turner NH, Partridge A, Sanna G, Di Leo A, Biganzoli L. Utility of gonadotropin-releasing hormone agonists for fertility preservation in young breast cancer patients: the benefit remains uncertain. Ann Oncol. 2013;24(9):2224–35.
142. Moore HC, Unger JM, Phillips KA, Boyle F, Hitre E, Porter D, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015;372(10):923–32.
143. Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. Fertil Steril. 2009;91(3):694–7.
144. Sverrisdottir A, Nystedt M, Johansson H, Fornander T. Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial. Breast Cancer Res Treat. 2009;117(3):561–7.
145. Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. JAMA. 2011;306(3):269–76.
146. Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the gbg 37 zoro study. J Clin Oncol. 2011;29(17):2334–41.
147. Munster PN, Moore AP, Ismail-Khan R, Cox CE, Lacevic M, Gross-King M, et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. J Clin Oncol. 2012;30(5):533–8.
148. Elgindy EA, El-Haieg DO, Khorshid OM, Ismail EI, Abdelgawad M, Sallam HN, et al. Gonadatrophin suppression to prevent chemotherapy-induced ovarian damage: a randomized controlled trial. Obstet Gynecol. 2013;121(1):78–86.
149. Morgan S, Anderson RA, Gourley C, Wallace WH, Spears N. How do chemotherapeutic agents damage the ovary? Hum Reprod Update. 2012;18(5):525–35.
150. Bildik G, Akin N, Senbabaoglu F, Sahin GN, Karahuseyinoglu S, Ince U, et al. Gnrh agonist leuprolide acetate does not confer any protection against ovarian damage induced by chemotherapy and radiation in vitro. Hum Reprod. 2015;30(12):2912–25.
151. Fasano G, Moffa F, Dechene J, Englert Y, Demeestere I. Vitrification of in vitro matured oocytes collected from antral follicles at the time of ovarian tissue cryopreservation. Reprod Biol Endocrinol. 2011;9:150.
152. Lee JA, Barritt J, Moschini RM, Slifkin RE, Copperman AB. Optimizing human oocyte cryopreservation for fertility preservation patients: should we mature then freeze or freeze then mature? Fertil Steril. 2013;99(5):1356–62.
153. Shalom-Paz E, Almog B, Shehata F, Huang J, Holzer H, Chian RC, et al. Fertility preservation for breast-cancer patients using ivm followed by oocyte or embryo vitrification. Reprod Biomed Online. 2010;21(4):566–71.
154. Oktay K, Oktem O. Fertility preservation medicine: a new field in the care of young cancer survivors. Pediatr Blood Cancer. 2009;53(2):267–73.

155. Thibaud E, Ramirez M, Brauner R, Flamant F, Zucker JM, Fekete C, et al. Preservation of ovarian function by ovarian transposition performed before pelvic irradiation during childhood. J Pediatr. 1992;121(6):880–4.
156. Cowles RA, Gewanter RM, Kandel JJ. Ovarian repositioning in pediatric cancer patients: flexible techniques accommodate pelvic radiation fields. Pediatr Blood Cancer. 2007;49(3):339–41.
157. Terenziani M, Piva L, Meazza C, Gandola L, Cefalo G, Merola M. Oophoropexy: a relevant role in preservation of ovarian function after pelvic irradiation. Fertil Steril. 2009;91(3):935 e915–36.
158. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update. 2001;7(6):535–43.
159. Katz DJ, Kolon TF, Feldman DR, Mulhall JP. Fertility preservation strategies for male patients with cancer. Nat Rev Urol. 2013;10(8):463–72.
160. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HWG, Behre HM, et al. World health organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231–45.
161. Jahnukainen K, Stukenborg JB. Clinical review: present and future prospects of male fertility preservation for children and adolescents. J Clin Endocrinol Metab. 2012;97(12):4341–51.
162. Agarwal A, Ong C, Durairajanayagam D. Contemporary and future insights into fertility preservation in male cancer patients. Transl Androl Urol. 2014;3(1):27–40.
163. Williams DH. Fertility preservation in the male with cancer. Curr Urol Rep. 2013;14(4):315–26.
164. Osterberg EC, Ramasamy R, Masson P, Brannigan RE. Current practices in fertility preservation in male cancer patients. Urol Ann. 2014;6(1):13–7.
165. Dumont L, Arkoun B, Jumeau F, Milazzo JP, Bironneau A, Liot D, et al. Assessment of the optimal vitrification protocol for prepubertal mice testes leading to successful in vitro production of flagellated spermatozoa. Andrology. 2015;3(3):611–25.
166. Radford J, Shalet S, Lieberman B. Fertility after treatment for cancer. Questions remain over ways of preserving ovarian and testicular tissue. BMJ. 1999;319(7215):935–6.
167. Pukazhenthi BS, Nagashima J, Travis AJ, Costa GM, Escobar EN, Franca LR, et al. Slow freezing, but not vitrification supports complete spermatogenesis in cryopreserved, neonatal sheep testicular xenografts. PLoS One. 2015;10(4):e0123957.
168. Johnson DH, Linde R, Hainsworth JD, Vale W, Rivier J, Stein R, et al. Effect of a luteinizing hormone releasing hormone agonist given during combination chemotherapy on posttherapy fertility in male patients with lymphoma: preliminary observations. Blood. 1985;65(4):832–6.
169. Shetty G, Meistrich ML. Hormonal approaches to preservation and restoration of male fertility after cancer treatment. J Natl Cancer Inst Monogr. 2005;34:36–9.

Pregnancy and Gastrointestinal Cancers

36

Irfan Cicin, Gulay Durmus Altun, Nermin Tuncbilek, Yavuz Atakan Sezer, and Ezgi Cisil Erdogan

Pregnancy and Gastrointestinal Cancers

The second most common cause of death for women in reproductive age is cancer. The mean age of mothers is on the rise today [1]. As the incidence of cancer rises with age, the incidence of cancer during pregnancy is expected to also rise. Cancer incidence during pregnancy is between 0.07% and 0.1%. In Europe, between 3000 and 5000 pregnant women are diagnosed with cancer annually, while in the United States of America, this number is 3500. The most common cancers during pregnancy are cervical cancer, breast cancer, melanoma, and lymphoma. Colorectal cancer is the 7th most common type of cancer diagnosed during pregnancy [2]. Just like the other types of cancer diagnosed during pregnancy, there are oncologic, obstetrical, ethical, religious, legal, and socioeconomic issues regarding the diagnosis and treatment of gastrointestinal cancer (Table 36.1). The well-being of the fetus and the mother must always be considered. There are contradictions as the treatment of the pregnant woman may harm the fetus. Working with a multidisciplinary team involving an obstetrician/perinatologist, a surgeon, a radiation oncologist, a medical oncologist, a radiologist, a social worker, a genetic counselor, and an ethicist is necessary for the diagnosis and treatment of gastrointestinal cancers during pregnancies.

Table 36.1 Managing cancer during pregnancy

Oncologic issues	Obstetrical issues	Other issues[a]
Therapy timing Therapy type Maternal effects of therapy Outcomes on the mother	Fetal effects of therapy Fetal monitoring Use of corticosteroids Amniocentesis Delivery time Delivery route	Termination of the pregnancy Fetal advocate Fetal viability Future fertility Cost of therapy Autonomy right

[a]Ethical, religious, legal, and socioeconomic issues

The 2 most important factors that need to be considered are the stage of cancer and pregnancy. Stages of pregnancy and fetal development should be well-known to find the appropriate treatment plan for both the patient and fetus. The location, type, and stage of the cancer and what the mother prefers are very important considerations.

Pregnancy Stages and Fetal Development

Pregnancy is divided into three stages: (1) the germinal stage, which is the first 2 weeks; (2) the embryonic stage, which is between the end of the 2nd week and 2nd month; and (3) the fetal stage, which is the remaining time until birth. During the germinal stage, cell division begins, implantation followed, and the embryonic disk is formed. The placenta is also formed during this stage. During those first 2 weeks, potential damage because of cancer therapy will cause the death of the embryo and spontaneous abortion. The second stage is the embryonic stage, and the developing baby is called an embryo. Embryogenesis is the first 60 days of the pregnancy, and this is the time during which the embryo forms and develops. From 2 to 4 weeks, the embryo travels down the fallopian tube into the uterus where it implants. The implantation is completed by the end of the 4th week. During the embryonic stage, the embryo is susceptible to drugs, infection, radiation, and nutritional deficiencies. The period after the 60th day until the birth is called organogenesis.

I. Cicin (✉)
Department of Medical Oncology, Trakya University, Edirne, Turkey

G. D. Altun
Department of Nuclear Medicine, Physiology, Trakya University Medical Faculty, Edirne, Turkey

N. Tuncbilek
Department of Radiology, Trakya University, Edirne, Turkey

Y. A. Sezer
Department of General Surgery, Trakya University Medical Faculty, Edirne, Turkey

E. C. Erdogan
Department of Medical Oncology, Trakya University Medical Faculty, Edirne, Turkey

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_36

This stage is the fetal stage, and the developing baby is now called a fetus [3].

Clinically, pregnancy has three trimesters each lasting 3 months. Exposure to systemic anticancer therapy in the first trimester may result in spontaneous abortion and fetal malformation in 20–30% and 10–25% of pregnancies, respectively. Embryogenesis is completed before the 2nd trimester starts. In 2nd and 3rd trimesters, the fetus is less susceptible to damage by teratogens. Systemic anticancer therapies after the first trimester most commonly result in low birth weight. A mother's dietary problems because of cancer treatment are thought to be responsible for the low birth weight in addition to the cytotoxic treatment itself. Cytotoxic therapy in the 2nd and 3rd trimesters results with intrauterine growth retardation, miscarriage, premature birth, and low birth weight in 20–40% of pregnancies [3, 4]. Possible effects of radiation for different gestational age are shown in Table 36.2 and Fig. 36.1.

Table 36.2 Possible effects of radiation on fetus at different gestational ages

Gestational age	Adverse effects	Dose
The 1st trimester (Before implantation: 0–2 weeks)	Lethal or no effect	50–100 mGy
The 2nd trimester (Organogenesis: 3–7 weeks)	Congenital anomalies and growth retardation	200–250 mGy
The 3rd trimester (Early fetal stage: 8–15 weeks)	High risk of mental retardation and microcephaly	50–310 mGy
Late fetal stage (16–25 weeks)	Low risk of mental retardation	250–280 mGy

Diagnostic and Staging Imaging and Pregnancy

Symptoms of gastrointestinal tract tumors such as nausea, vomiting, abdominal pain, change in bowel habits, and rectal bleeding are also among physiological changes seen during pregnancy and often interpreted as such by both the clinician and the patient. Due to the potential risks of X-ray usage on the fetus, further investigation is usually not carried out. However, many pregnant women are exposed to ionizing radiation for diagnostic reasons or treatment. The number of anomalies that may present in the fetus depends on the radiation dose and stage of pregnancy. The period between the 18th and 38th days of pregnancy is when the embryo develops

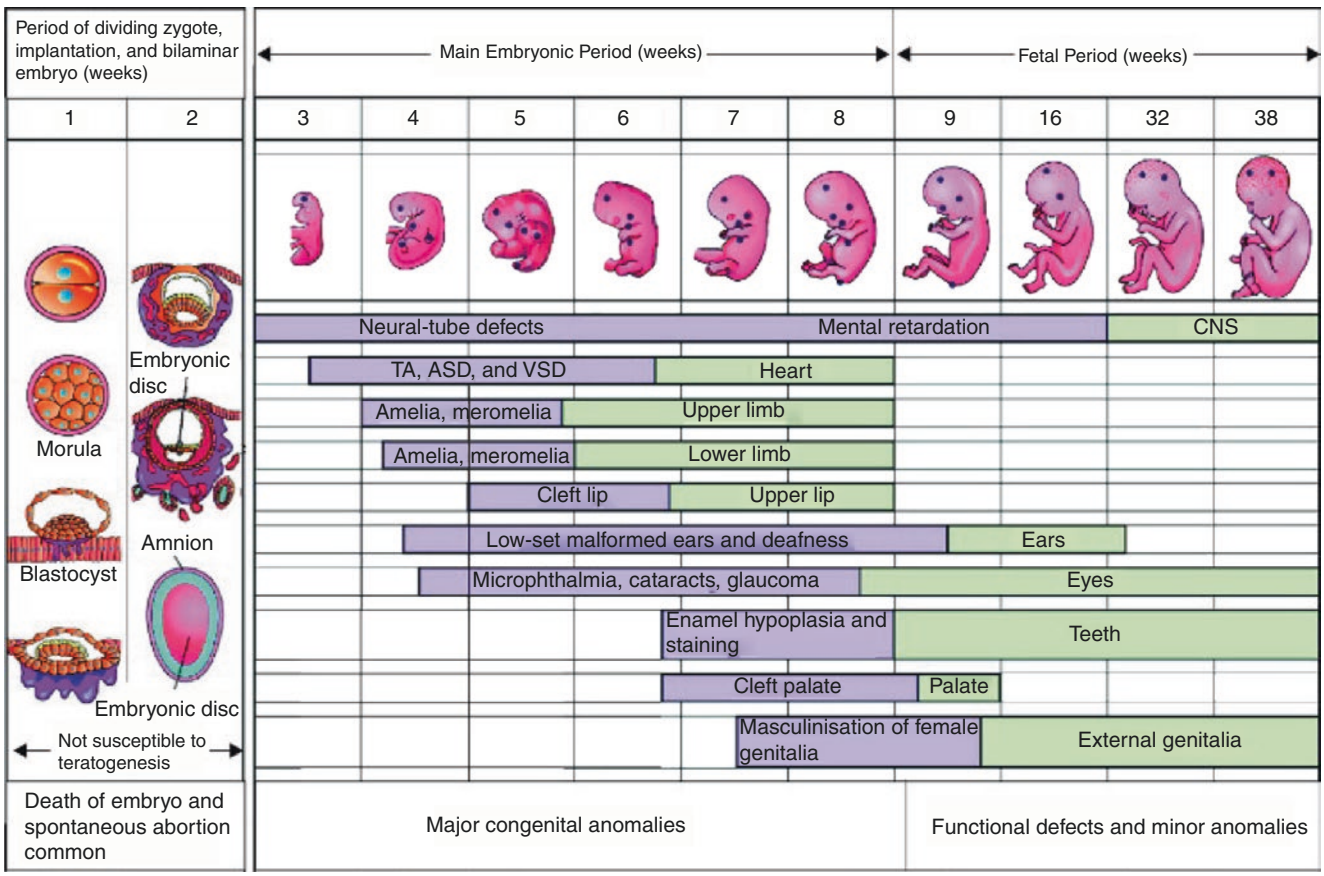


Fig. 36.1 Possible effects of radiation for different gestational ages. (Reprinted with permission from Cardonick and Iacobucci [3])

to fetus. In this period, the fetus is the most sensitive to the radiation, and in choosing the best imaging tool, the safety of fetus must be considered. In diagnostic radiological procedures, the fetus is exposed to a dose of radiation lower than 1 rad. Recent studies show that radiation dose harmful to a fetus is above 50 mGy (5 rad), and most of the diagnostic tools do not exceed that dose level [1]. Before using diagnostic tools or treatments that expose radiation, a pregnancy test must be done in women of childbearing age. Also pregnant women should be informed about the possible effects on the fetus, and the benefit of both the mother and fetus must be taken into consideration [5].

Pregnancy tests are performed routinely for oncologic female patients in reproductive age. If the patient is pregnant, diagnostic nuclear medicine procedures should be avoided as much as possible. None of the radionuclide treatment options is safe for pregnant patients. Treatment should be delayed until the baby is born or the pregnancy is terminated. Along with dose-dependent changes induced by ionizing radiation, there are cytotoxic effects independent of dose. There are studies that show intrauterine radiation exposure increasing leukemia incidence [6].

According to the 1977 report of the National Council on Radiation Protection and Measurements (NCRP), exposure to radiation less than a dose of 50 mGy is negligible. The risk of malformation has been reported to increase above control levels of 150 mGy [7]. Therefore, any effect on a fetus due to radiation exposure from diagnostic procedures is very rare. However, radiation accidents or therapeutic radionuclide use is very dangerous for the fetus. It should also be kept in mind that the risk of spontaneous abortion is 15%, prematurity and growth retardation 4%, major malformation 3%, and mental retardation 1% in normal pregnancy [8].

Radiological Diagnosis

The study conducted by Ueo et al. is one of the largest studies on this subject. Out of 61 pregnant patients with gastric cancer, 96.7% were in advanced stage at the time of diagnosis [9]. Delayed diagnosis and advanced-stage presentation of the patients are the most important factors that have a negative influence on the prognosis.

Diagnostic tools for colorectal cancer in pregnant patients are very similar with non-pregnant patients [10]. To detect liver metastases, abdominal ultrasounds should be performed. Abdominal computed tomography (CT) scan should be avoided during the first trimester of pregnancy due to the radiation exposure. Colonoscopy with a biopsy is the only way to make a definitive diagnosis [11]. However, risk of fetal hypoxia associated with maternal hypoxia, uterine pressure rise, placental rupture, and intestinal perforation should be taken into consideration for colonoscopy during pregnancy [12, 13]. Colonoscopy for left-side tumors is safe. For right-side tumors, risks can be minimized if the colonoscopy is performed in the left lateral decubitus position with careful manipulation, maternal nasal oxygen administration, and cardiotocography monitor [14, 15].

The first step in the diagnosis of GI cancer during pregnancy should be ultrasound. However, the last 10 years has seen a gradual increase in the use of CT with contrast for staging and to detect metastasis during pregnancy [16, 17].

The control dose for modern CT scanners, which use automated exposure, is around 13 mGy [18, 19]. During pregnancy, intravenous (IV) and oral iodine-based contrasts can be used. Iodinated contrast agents barely cross the placenta and enter fetal circulation. Fetal toxicity has not been observed in patients or in experimental studies. Thyroid disorders in newborns have not been reported [7]. CT imaging is contraindicated due to teratogenicity, especially in the first trimester. In early organogenesis, a radiation dose of 0.05 Gy can cause mental retardation. In late organogenesis, which is after the 16th week, a radiation dose of 0.06–0.31 Gy can cause microcephaly and mental retardation. The risk of carcinogenesis rises in childhood and the adolescent period if there is prenatal radiation exposure [20, 21]. Fetal radiation doses are shown in Table 36.3 [20, 21].

Ultrasound and magnetic resonance imaging (MRI) can be alternatives to avoid the radiation in pregnant women with GI cancers. However, ultrasound compared to abdominal CT has lower sensitivity. Ultrasound can be used transrectally for staging of rectal tumors [22]. A fetus is not exposed to radiation with MRI, but it is exposed to the magnetic field, which is more than 10,000 times greater than that of Earth. The effect of MR imaging on a fetus, especially in the first trimester, is still unknown [23, 24]. In all trimesters, MRI at 1.5 Tesla or less is not considered problematic. MRI at 3.0 T has not been proven safe, and MRI at 1.5 T or less should be used for pregnant patients. IV contrast agents are avoided, especially in the first trimester, since they can access fetal circulation. If there is an indication, a non-contrast 1.5 T MR imaging would be safe to use [20, 23, 25].

Endoscopic biopsy should be the first choice if there are prolonged and treatment-resistant gastrointestinal symptoms in pregnancy [26]. According to the American Society of

Table 36.3 Fetal radiation doses with abdominal imaging [20, 21]

Imaging test	Fetal radiation dose (mGy)
Abdominal radiography (Low to moderate dose examinations)	0.1–3
Fluoroscopy (Low to moderate dose examinations)	1–10
Pelvic CT (High dose)	9.4
Abdominal CT (High dose)	8

CT computed tomography

Gastrointestinal Endoscopy Guidelines: If therapeutic intervention is desired, instead of radiologic or surgical interventions, endoscopy is a safer alternative if clinically appropriate. If possible, it should be performed in the 2nd trimester. Due to maternal oversedation, hypoventilation, hypotension, or maternal positioning, precipitating uterine hypovascularization and fetal hypoxia can develop. Teratogenic effects associated with sedative agents and premature birth risk should also be considered.

Nuclear Medicine

Accurate staging of malignant tumors in pregnant women is crucial just like it is for non-pregnant women. The presence and location of tumors determine therapy and prognosis. Therefore, functional imaging tools such as ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT, FDG-PET/MR, and MR with diffusion-weighted imaging open new horizons in oncological imaging. The use of CT and FDG-PET/CT staging examinations in oncology patients has grown rapidly during the past decade. However, CT and FDG-PET/CT examinations are associated with substantial exposure to ionizing radiation. The exposure of a single whole-body FDG-PET/CT examination is 8–20 mSv in adult women (0.013–0.031 mSv/MBq) [27]. Most of the procedures are not a significant risk to the fetus. However, some of the radiopharmaceutical compounds may pose a significant risk to the developing baby. Still, most of them deliver acceptable amounts of radiation doses [27]. Radiation-absorbed doses to the fetus for different stages of pregnancy can be found in Table 36.4.

Cancer Treatment Modalities

There are oncological, obstetrical, ethical, legal, and socioeconomic issues for cancer treatment during pregnancy. Effects of treatment on both the mother and the fetus must be considered [28]. Among the gastrointestinal cancers, colorectal cancer is the most common [29]. Gastric cancer is very rare, with approximately 136 reported cases in the literature [30]. Pancreatic cancer and hepatoma are even rarer [31, 32]. For gastrointestinal cancer in pregnant women, there are no special guidelines. The treatment is different for every patient and customized according to the gestational age and cancer stage.

Table 36.4 Radiation dose absorbed by the fetus during different stages of pregnancy

Stage of pregnancy	^{18}F- FDG	^{99m}Tc- MDP
Early	0.0180	0.0061
3 months	0.0180	0.0054
6 months	0.0160	0.0027
9 months	0.0150	0.0024

^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{99}mTc-MDP, technetium-99-methylene diphosphonate

Systemic Therapy

Conventional cytotoxic drugs do not only affect cancer cells but also healthy cells. Chemotherapy agents can also cross placenta and affect the fetus since they have low molecular weight. Still, most patients who decide not to terminate the pregnancy are treated with chemotherapy. With the use of chemotherapy in the first trimester, risks of malformation, spontaneous abortion, and fetal death increase. All chemotherapy agents are teratogenic for animals. Teratogenic effects on humans for most of the agents are unknown. Teratogenic effects depend on gestational week, dosage, and the agent used [33]. For the first trimester, malformation risk after chemotherapy exposure is estimated at 10–20%. For the second and third trimesters, major malformations are thought to have no association with chemotherapy exposure [3]. But these agents may increase the risk of intrauterine growth restriction (IUGR) and low birth weight [34]. Pregnancy categories of chemotherapy agents and targeted cancer therapies used in gastrointestinal cancer are shown in Tables 36.5 and 36.6. As there are no longitudinal follow-up of these

Table 36.5 Pregnancy categories of chemotherapy agents used in gastrointestinal cancer and studies on humans/animals

	Studies on animals	Studies on humans	Pregnancy category
Cisplatin	T*	++	D
Carboplatin	T	+++	D
Gemcitabine	T*	++	D
Oxaliplatin	T*	+++	D
Fluorouracil	T	+++	D
Irinotecan	T*	+	D
Epirubicin	T*	+++	D
Docetaxel	T*	+++	D
Paclitaxel	T	+++	D
Capecitabine	T*	+	D

T Teratogenic
*T** Data suggesting teratogenicity is not strong enough
(+ in some cases, ++ in case series with small number of patients, +++ There are studies on other cancers as well as gastrointestinal cancer)

Table 36.6 Pregnancy categories of targeted cancer therapies used for gastrointestinal cancer and studies on humans/animals

	Studies on humans	Studies on animals	Pregnancy category
Bevacizumab	ND	T	C
Cetuximab	ND	T*	C
Panitumumab	ND	T	C
Sorafenib	ND	T	D
Imatinib	ND	T	D

T Teratogenic
*T** Data suggesting teratogenicity is not strong enough
ND No data

babies born to treated mothers, long-term effects of chemotherapy are not fully established.

Systemic chemotherapy should not be started in the first trimester. Many chemotherapy agents other than methotrexate can be used safely during the second and third trimesters. Doxorubicin and epirubicin can be used safely during the second and third trimesters [35]. Except for a few cases, taxane use has not been shown to cause congenital anomalies. Compared to carboplatin, cisplatin has more side effects on the fetus [3]. Weekly chemotherapy sessions may be a better approach when delivering chemotherapy during pregnancy. Thus, pregnancy can be monitored closely, and drugs can be stopped if needed. If the fetus is conceived during the treatment, course of the treatment is uncertain. Exposure for the first 2–3 weeks is not associated with teratogenicity but with the risk of miscarriage. If there is a long-term exposure to drugs, the patient should be informed about congenital anomalies and possibly abortion [3].

Radiation Therapy

High-energy X-rays are used to kill cancer cells when using radiation therapy, and this can harm the fetus in all three trimesters of pregnancy. Radiation therapy is not recommended during the first trimester because it is the time when the major organs and nervous system start to develop. The safety of radiation therapy in the second and third trimesters is dependent on the location of the tumor and the radiation dose. In general, the use of radiation therapy should be avoided during the pregnancy. Women should be advised to wait until delivery of the baby, especially when tumors are mostly located in the pelvis [36].

Surgery

Surgery is the safest treatment of cancer for the fetus. Improvements in surgery and anesthetics make surgery a relatively safe and effective option for treatment during pregnancy despite the risks associated with it. If a surgically resectable tumor is diagnosed after the 20th week of pregnancy, surgery can be postponed until after the birth. Delivery may be delayed until the 28th to 32nd weeks for the lung maturation of the fetus. If there is bowel obstruction, a diverting colostomy is recommended until the birth and then definitive therapy can be provided. As for the delivery route, vaginal delivery is preferred if the tumor is not obstructing the pelvis. If caesarean delivery is planned, resection of the tumor can be done right after birth. If a tumor is diagnosed before the 20th week of pregnancy, surgery may be done without disturbing the gravid uterus [37]. However, gastrointestinal cancers diagnosed before the 20th week of the pregnancy remain very rare, so there is not enough data on surgical safety on the fetus. In exceptional situations, hysterectomy or termination of the pregnancy may be needed.

If surgery during pregnancy is selected, minimally invasive procedures such as laparoscopic surgery are considered to be more reliable and safer than open conventional surgery. The advantages of laparoscopic surgery for pregnant women are similar to non-pregnant women. With laparoscopic procedures, there is less discomfort, pain, or scarring after the surgery, and the recovery time is somewhat shorter. In addition, the incidence of thromboembolism compared to open surgery is lower. Fetal acidosis due to intraperitoneal CO_2 insufflation, preterm birth, placental rupture, reduced uteroplacental blood flow due to the high intraperitoneal pressure, and fetal hypoxia are among the major complications of laparoscopy during pregnancy, but those data are not supported with high-quality recommendations. Recent data support that laparoscopic surgery should be postponed in first trimester to second trimester and in third trimester to after delivery, but these recommendations are not supported with strong evidence and have been left with only expert opinions. The current data support that laparoscopy can be performed safely in all trimesters with similar risks to conventional surgery [37]. Surgery and/or laparoscopic surgery during pregnancy is not a one-man show; on the other hand is a multidisciplinary team work. Preoperative work-up for patient preparation, anesthesia during surgery in pregnant woman, and fetus monitoring are basic and mandatory corner stones of surgical treatment in pregnant women. The surgeon's skill and experience are important, and especially surgeon should be familiar with laparoscopic surgery in non-pregnant women and should be a member and leader of a multidisciplinary team consisting of gynecologist, oncologist, pediatrician, radiologist, and perinatologist in order to reduce maternal and fetal complications.

Other Issues

Breastfeeding is not advised if the woman with a cancer diagnosis is actively receiving chemotherapy because chemotherapeutic agents can transfer to the breast milk and so to the baby. Thus, for all women receiving cytotoxic, hormonal, and targeted treatments, breastfeeding is contraindicated. Mothers are advised to wait at least 2–4 weeks before breastfeeding after the chemotherapy is stopped [38].

Placental metastasis is very rare. There have been less than 100 cases reported in the last decades, and metastasis to the fetus has been seen in only 15% of those cases. However, those numbers are not reliable since there is no routine histological examination of placentas. Gastrointestinal cancer is the 5th most common cancer with placental metastasis. The incidence of placental metastasis in different types of cancers is shown in Table 36.7 [38].

Table 36.7 Incidence of placental metastasis in different types of cancers

Type of cancer	Placental metastasis
Melanoma	28
Breast Cancer	14
Lung Cancer	13
Leukemias	10
Lymphomas	7
Gastrointestinal Cancer	9
Sarcomas	8
Head Neck Cancer	3
Ovarian Cancer	2
Carcinoma of Unknown Primary	2
Cervical Cancer	1
Adrenal Cancer	1

Conclusion

The incidence of cancer during pregnancy is a very difficult problem for both fetus and mother. There are oncologic, obstetrical, ethical, religious, legal, and socioeconomic issues regarding the diagnosis and treatment of cancer. There is a need for more information about this issue. However, it is impossible to make clinical trials for pregnancy with cancer. Multicenter cohort studies are needed. This issue will continue to be complex during the era of targeted therapy and immunotherapy.

Obstetricians/perinatologists, surgeons, radiation oncologists, medical oncologists, radiologists, genetic counselors, and ethicists should work in multidisciplinary teams for the diagnosis and treatment of gastrointestinal cancers during pregnancies.

References

1. Mathews TJ, Hamilton BE. First births to older women continue to rise. NCHS data brief, no 152. Hyattsville, MD: National Center for Health Statistics; 2014.
2. Woods JB, Martin JN Jr, Ingram FH, Odom CD, Scott-Conner CE, Rhodes RS. Pregnancy complicated by carcinoma of the colon above the rectum. Am J Perinatol. 1992;9(2):102–10.
3. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol. 2004;5:283–91.
4. Backes CH, Moorehead PA, Nelin LD. Cancer in pregnancy: fetal and neonatal outcomes. Clin Obstet Gynecol. 2011;54(4):574–90.
5. Bural GG, Laymon CM, Mountz JM. Nuclear imaging of a pregnant patient: should we perform nuclear medicine procedures during pregnancy? Mol Imaging Radionucl Ther. 2012;21(1):1–5.
6. Bithell JF, Stone RA. On statistical methods for analysing the geographical distribution of cancer cases near nuclear installations. J Epidemiol Community Health. 1989;43(1):79–85.
7. McCollough CH, Schueler BA, Atwell TD, Braun NN, Regner DM, Brown DL, et al. Radiation exposure and pregnancy: when should we be concerned? Radiographics. 2007;27:909–17.
8. Wang PI, Chong ST, Kielar AZ, Kelly AM, Knoepp UD, Mazza MB, et al. Imaging of pregnant and lactating patients: part I, evidence-based review and recommendations. AJR Am J Roentgenol. 2012;198(4):778–84.
9. Ueo H, Matsuaka H, Tamura S. Prognosis in gastric cancer associated with pregnancy. World J Surg. 1991;15:293–7.
10. Kraljevic M, Hoffmann H, Knipprath A, von Holzen U. Obstructing adenocarcinoma of the descending colon in a 31-year-old pregnant woman. Int J Surg Case Rep. 2014;5(12):958–60.
11. Khodaverdi S, Kord Valeshabad A, Khodaverdi M. A case of colorectal cancer during pregnancy: a brief review of the literature. Case Rep Obstet Gynecol. 2013;2013:626393.
12. Minter A, Malik R, Ledbetter L, Winokur TS, Hawn MT, Saif MW. Colon cancer in pregnancy. Cancer Control. 2005;12(3):196–202.
13. Yaghoobi M, Koren G, Nulman I. Challenges to diagnosing colorectal cancer during pregnancy. Can Fam Physician. 2009;55(9):881–5.
14. Cappell MS, Colon VJ, Sidhom OA. A study at 10 medical centers of the safety and efficacy of 48 flexible sigmoidoscopies and 8 colonoscopies during pregnancy with follow-up of fetal outcome and with comparison to control groups. Dig Dis Sci. 1996;41:2353–61.
15. Kocian PA, Hoch J, Halaska M. Sigmoid colon cancer in pregnancy –a case report. Rozhl Chir. 2015;94(4):170–3.
16. Lazarus E, Debenedectis C, North D, Spencer PK, Mayo-Smith WW. Utilization of imaging in pregnant patients: 10-year review of 5270 examinations in 3285 patients—1997–2006. Radiology. 2009;251(2):517–24.
17. Long SS, Long C, Lai H, Macura KJ. Imaging strategies for right lower quadrant pain in pregnancy. AJR Am J Roentgenol. 2011;196:4–12.
18. Huda W. Review of radiologic physics. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
19. Wieseler KM, Bhargava P, Kanal KM, Vaidya S, Stewart BK, Dighe MK. Imaging in pregnant patients: examination appropriateness. Radiographics. 2010;30:1215–29; discussion 1230–33
20. Tremblay E, Thérasse E, Thomassin-Naggara I, Trop I. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. Radiographics. 2012;32(3):897–911.
21. Chen MM, Coakley FV, Kaimal A, Laros RK Jr. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstet Gynecol. 2008;112(2 pt 1):333–40.
22. Voulgaris E, Pentheroudakis G, Pavlidis N. Cancer and pregnancy: a comphrehensive review. Surg Oncol. 2011;20:175–85.
23. Kanal E. Pregnancy and the safety of magnetic resonance imaging. Magn Reson Imaging Clin N Am. 1994;2(2):309–17.
24. Strasilova P, Prochazka M, Pilka R. Maligni tumory v tehotenství. Postgraduaní medicina. 2014;5:52–61.
25. De Wilde JP, Rivers AW, Price DL. A review of the current use of magnetic resonance imaging in pregnancy and safety implications for the fetus. Prog Biophys Mol Biol. 2005;87(2–3):335–53.
26. Qureshi WA, Rajan E, Adler DG, Davila RE, Hirota WK, Jacobson BC, et al. ASGE Guideline: guidelines for endoscopy in pregnant and lactating women. Gastrointest Endosc. 2005;61:357–62.
27. Xie T, Zaidi H. Development of computational pregnant female and fetus models and assessment of radiation dose from positron-emitting tracers. Eur J Nucl Med Mol Imaging. 2016;43(13):2290–300.
28. Mazze RI, Källén B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol. 1989;161(5):1178–85.
29. Nesbitt JC, Moise KJ, Sawyers JL. Colorectal carcinoma in pregnancy. Arch Surg. 1985;120:636.
30. Barbosa OA, Souza AD, Moura MR, Junior EJ, Fontenele JP. Diffuse gastric cancer during pregnancy: report of a rare association. World J Oncol. 2015;6(5):456–8.
31. Davis J, Bashir S, Wubneh H, Borum ML. Metastatic pancreatic adenocarcinoma during pregnancy. ACG Case Rep J. 2016;3(4):e190.
32. Choi KK, Hong YJ, Choi SB, Park YN, Choi JS, Lee WJ, Kim KS. Hepatocellular carcinoma during pregnancy: is hepatocellular carcinoma more aggressive in pregnant patients? J Hepatobiliary Pancreat Sci. 2011;18(3):422–31.

33. Amant F, Vandenbroucke T, Verheecke M, Fumagalli M, Halaska MJ, Boere I, International Network on Cancer, Infertility, and Pregnancy (INCIP), et al. Pediatric outcome after maternal cancer diagnosed during pregnancy. N Engl J Med. 2015;373(19):1824–34.
34. Karnaofsky DA. Drugs as teratogens in animals and man. Annu Rev Pharmacol. 1965;5:447.
35. Koren G, Carey N, Gagnon R, Maxwell C, Nulman I. Cancer chemotherapy and pregnancy. J Obstet Gynaecol Can. 2013;35(3):263–78.
36. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. Lancet Oncol. 2005;6(5):328–33.
37. Geisler JP, Rose SL, Mernitz CS, Warner JL, Hiett AK. Nongynecologic laparoscopy in second and third trimester pregnancy: obstetric implications. JSLS. 1998;2(3):235–8.
38. ESMO E-Learning: Cancer Management During Pregnancy. http://oncologypro.esmo.org/content/download/38057/749465/file/cancer-pregnancy-Pavlidis-Boussios-Pentheroudakis.pdf. Last accessed 19 Jan 2018.

Vaccination in Patients with a Gastrointestinal Cancer

37

Şehnaz Alp and Murat Akova

Introduction

Cancer patients are remarkably vulnerable to infectious diseases as a consequence of impaired host defenses; immunosuppressive characteristics of the disease or its treatment; and increased potential of exposure to pathogens due to frequent medical care requirements. Reducing the incidence of vaccine-preventable diseases has a favorable impact on the morbidity and mortality in oncology patients. Hence, vaccination is recommended as a part of standard of care of these patients [1–5]. The risk of infection and the ability to mount a protective immune response to a vaccine are closely related to the degree of immunosuppression resulting from the severity of the disease or administration of chemotherapy or radiation therapy. The immune response to vaccines in cancer patients cannot be predicted, but tends to be less potent than healthy individuals. However, vaccination may still provide significant clinical benefits in this patient population. A favorable protection may also require additional strategies such as passive immunization or prophylactic measures such as antiviral prophylaxis during influenza A outbreaks [1, 6].

Definition of the Degree of Immunosuppression

The degree of immune impairment is usually categorized as high- and low-level immunosuppression. High-level immunosuppressed patients are those having combined primary immunodeficiency disorder; receiving cancer chemotherapy; human immunodeficiency virus (HIV)-infected adults with CD4 T-lymphocyte count < 200 cells/mm^3; solid organ transplantation recipients within 2 months after transplant; patients receiving corticosteroid therapy with a dose of ≥20 mg/day of prednisone or equivalent for ≥14 days; or patients receiving tumor necrosis factor-alpha (TNF-α[alpha]) inhibitors or rituximab (anti-CD20 monoclonal antibodies). In hematopoietic stem cell transplantation (HSCT) recipients, the degree of immunosuppression depends on the type of transplant, source of stem cell, type of donor, and presence and treatment of graft-versus-host disease (GVHD) [7, 8].

Patients with low-level immunosuppression are those receiving corticosteroid therapy lower than 20 mg/day of prednisone or equivalent for ≥14 days or receiving alternate-day regimen; HIV-infected adults with CD4 T-lymphocyte count of 200–499 cells/mm^3; and those taking methotrexate (MTX) with a dose of ≤0.4 mg/kg/week or azathioprine ≤3 mg/kg/day, or 6-mercaptopurine ≤1.5 mg/kg/day [7].

Safety of Vaccination in Immunosuppressed Individuals

Vaccines are classified into two groups: live or inactivated vaccines. Available data indicate that safety profiles of inactivated vaccines are nearly the same in both immunocompetent and immunocompromised individuals [7, 9]. Nevertheless, immunocompromised patients are most likely to have reduced immune response to vaccination [6, 7, 9]. Immunization with live viral vaccines may result in proliferation of attenuated vaccine strains. Accordingly, live vaccines are usually contraindicated in immunosuppressed patients [6, 7].

While deciding whether or not to administer a vaccine to an immunocompromised patient, the balance between the risks and benefits should be evaluated considering the risk of vaccine-preventable disease; the risk of infection due to the vaccine strain; and the risk of vaccine-related side effects [7].

Ş. Alp
Department of Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine, Sihhiye, Ankara, Turkey

M. Akova (✉)
Department of Infectious Diseases and Clinical Microbiology, Hacettepe University School of Medicine, Sihhiye, Ankara, Turkey
e-mail: makova@hacettepe.edu.tr

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_37

Timing of Immunization

If possible, vaccines should be administered prior to the planned immunosuppressive medications, chemotherapy, radiation therapy, or splenectomy. Live viral vaccines can be administered at least 4 weeks before immunosuppression, but should be avoided during administration of chemotherapy regimens, and should not be given within 2 weeks of initiation of immunosuppression. Inactivated vaccines should be applied at least 2 weeks prior to immunosuppression. Both inactivated vaccines and live viral vaccines for varicella, and measles, mumps, and rubella (MMR) can be administered according to the recommended schedule to patients whose disease is in remission and the last chemotherapy cycle was completed at least 3 months previously. If anti-B-cell antibodies are included in the chemotherapy regimen, vaccination should be postponed at least 6 months. In case of immune globulin product replacement, vaccination should be deferred for a particular interval specific to each product [6, 7, 10].

Administration of vaccines during cancer chemotherapy should not be considered as valid doses unless protective antibody titers are documented. In such cases, revaccination should be performed after immune recovery [6, 7].

Vaccination in Adults with Solid Cancer

The following recommendations are principally based on the "2013 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for Vaccination of the Immunocompromised Host" prepared by an international panel of experts to provide evidence-based suggestions on immunization of patients with altered immune status and their household contacts [7]. Moreover, '2016 Adult Immunization Schedule approved by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians, the American College of Physicians, the American College of Obstetricians and Gynecologists, and the American College of Nurse-Midwives' on the use of licensed vaccines primarily for people living in the United States (updated and published annually) is proposed providing that the scheme is adapted to the principles on the timing and safety of immunization practices in immunocompromised individuals [10].

Influenza Vaccination

Clinical studies have reported high mortality rates (exceeding 30%) due to influenza among high-risk oncology patients [1, 5, 11–15]. The rates of seroconversion following inactivated influenza vaccine in patients with cancer usually range between 24% and 78% [6, 16–18]. As expected, immune response to influenza vaccine is closely related to the administered chemotherapy regimen and timing of vaccination within the chemotherapy cycle [6]. Even though a recent meta-analysis revealed that the rates of seroconversion and protection in cancer patients after inactivated influenza vaccine were nearly one-third of those in immunocompetent individuals [19], in some studies, the rates of seroconversion in oncology populations after influenza vaccination seem to be comparable to those in healthy controls [1, 3, 17, 20–23]. Moreover, influenza vaccination was associated with a significant decrease in influenza-like illness in a cohort of children with cancer in remission state [19].

Inactivated influenza vaccine is recommended annually for patients with hematological malignancies or with solid tumors, unless they receive anti-B-cell antibodies or intensive chemotherapy. If the patient is receiving anti-B-cell antibodies, vaccine administration should be delayed at least 6 months, because a poor response to the vaccine is anticipated [7]. Some authors favor administering an inactivated influenza vaccine to patients receiving intensive chemotherapy (e.g., induction or consolidation regimen for acute leukemia) to protect them against seasonal influenza strains [6].

Given the high case fatality rates, in certain circumstances, vaccination should be considered along with prophylactic measures to protect against influenza [1, 6]. Antiviral prophylaxis should be considered for patients receiving intensive chemotherapy who have contact with an influenza case within 48 h, or if the vaccine strains and the circulating seasonal influenza strains do not match [6].

Live attenuated influenza vaccine should not be administered to immunocompromised individuals [7].

Pneumococcal Vaccination

Streptococcus pneumonia is one of the most common pathogens causing pneumonia and sepsis in oncology settings [1]. Immunocompromising conditions as indications for pneumococcal vaccination are congenital or acquired immunodeficiency, HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, chronic renal failure, nephrotic syndrome, generalized malignancy, solid organ transplantation, iatrogenic immunosuppression (due to systemic corticosteroids, cancer chemotherapy, or radiation therapy), and anatomical or functional asplenia (sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, splenic dysfunction, and splenectomy) [10]. Even though it was reported that administration of multivalent pneumococcal conjugate

vaccine to cancer patients resulted in protective antibody titers nearly as high as those of healthy controls [1, 3, 22, 24], most patients receiving radiation therapy or myeloablative regimens and those with B-cell malignancies tend to have suboptimal immune responses [1, 3, 25–29]. Pneumococcal vaccine should be administered at least 2 weeks before immunosuppressive therapy or elective splenectomy. Vaccination during intense chemotherapy can result in a poor response [6].

Patients who have not previously been vaccinated with 13-valent pneumococcal conjugate vaccine (PCV13) or 23-valent pneumococcal polysaccharide vaccine (PPSV23) should receive PCV13 followed by PPSV23 at least 8 weeks apart. A second dose of PPSV23 should be given at least 5 years after the first dose of PPSV23. For patients who have previously been vaccinated with one dose of PPSV23, a single-dose PCV13 should be administered at least 1 year after the first dose of PPSV23. A second dose of PPSV23 should be given at least 8 weeks after PCV13 and no sooner than 5 years after the last dose of PPSV23 [6, 7, 10]. Patients who have not received PCV13 but have been vaccinated with 2 doses of PPSV23 should receive PCV13 at least 1 year after the last dose of PPSV23. For patients who have had PCV13 vaccination but not PPSV23, the first dose of PPSV23 should be administered at least 8 weeks after PCV13. A second dose of PPSV23 should be given 5 years after the first dose of PPSV23. If a patient has received PCV13 and 1 dose of PPSV23, a second dose of PPSV23 should be performed at least 8 weeks after PCV13 and no sooner than 5 years after the first dose of PPSV23 [10].

Haemophilus Influenza Type B (Hib) Vaccination

Children with malignancies have an increased risk of developing *Haemophilus influenzae* type b (Hib) infection as compared to healthy children [30]. Adult cancer patients, other than HSCT recipients, do not seem to have such a great risk. While Hib conjugate vaccine is indicated for children with cancer, it is not routinely recommended to adult cancer patients unless they undergo HSCT [6]. However, 1 dose of Hib vaccine is recommended to patients with anatomical or functional asplenia or sickle cell disease or to those for which an elective splenectomy is planned if they have not been previously vaccinated with Hib vaccine [10]. Vaccination for Hib should be administered more than 2 weeks prior to or more than 3 months after treatment with myeloablative regimens and/or radiation therapy, and preferably at least 2 weeks before splenectomy. With the use of this strategy, the level of antibody titers achieved in cancer patients tends to be comparable to those in healthy individuals [1, 3, 10, 25, 31].

Varicella Vaccination

The morbidity and mortality rates of primary varicella infection are high in seronegative cancer patients. Varicella vaccination with a two-dose schedule at least 4 weeks apart is recommended to adult patients without evidence of immunity to varicella at least 4 weeks before initiation of immunosuppressive therapy. Evidence of varicella immunity in adults refers to serologic evidence of immunity or laboratory-confirmed disease; history of varicella or herpes zoster diagnosed or verified by a health-care provider; US-born before 1980 (except health-care personnel and pregnant women); and documentation of varicella vaccination in two doses at least 4 weeks apart [7, 10]. Varicella vaccine should not be administered to highly immunocompromised patients. As with other viral vaccines, varicella vaccine can be administered to cancer patients whose disease is in remission and who have not received chemotherapy for at least 3 months [6, 7, 9].

Zoster Vaccination

Cancer patients have an increased risk of herpes zoster [6, 32]. A single dose of zoster vaccine is recommended to patients $\geq$ 60 years of age if it can be administered at least 4 weeks before initiation of immunosuppressive therapy [7, 10]. It should be considered for varicella-positive patients aged 50–59 years provided that it can be given at least 4 weeks before immunosuppressive therapy. Zoster vaccine is contraindicated in oncology patients receiving chemotherapy, but can be administered to cancer patients whose disease is in a remission state and whose last chemotherapy or radiation therapy was at least 3 months previously [6, 7, 9].

Measles, Mumps, Rubella (MMR) Vaccination

Adults born in 1957 or later should have a report of receipt of 1 or more doses of MMR vaccine or laboratory-documented immunity to measles, mumps, and rubella. For both the measles and mumps component, a routine second dose of MMR vaccine, administered at least 4 weeks after the first dose, is recommended for students in postsecondary education institutions; those who work in a health-care facility; or for international travelers [10].

Oncology patients infected with measles have high mortality rates [6, 33]. MMR vaccine should be administered as indicated and scheduled in the current guidelines [10], but should not be given during chemotherapy. However, it may be given to cancer patients whose disease is in a remission state and at least 3 months have passed after the last chemotherapy cycle [6].

Hepatitis A Vaccination

Cancer patients with indications for hepatitis A vaccination as stated in the current guidelines and those asking for protection from hepatitis A virus infection should receive hepatitis A vaccine [10]. Single-antigen vaccines are administered in 2 doses 6–12 months or 6–18 months apart in accordance with the prescribed vaccine. Hepatitis A and hepatitis B vaccine can be administered concomitantly. If combined hepatitis A and hepatitis B vaccine will be used, a 3-dose schedule at 0, 1, and 6 months should be administered; or alternatively a 4-dose schedule at 0, 7, and 21–30 days followed by a booster dose at 12 months can be used. Vaccine efficacy may be lower in oncology patients [6, 10].

Hepatitis B Vaccination

Cancer patients who have indications for hepatitis B vaccination as stated in the current guidelines, and those who are willing to receive hepatitis B vaccine should be immunized against hepatitis B [6, 10, 34]. Hepatitis B vaccination in 3-dose series should be completed. At least 1 month after the first dose, the second dose should be given and followed by the third dose at least 2 months after the second dose and at least 4 months after the first dose. Coadministration of hepatitis B and hepatitis A vaccine is feasible if hepatitis A vaccine is also indicated or requested. If combined hepatitis B and hepatitis A vaccine will be used, a 3-dose schedule at 0, 1, and 6 months should be administered; or alternatively a 4-dose schedule on 0, 7, and 21–30 days followed by a booster dose at 12 months may be used [6, 10]. Adult patients with immunocompromising conditions or hemodialysis patients should receive 1 dose of 40 mcg/mL (Recombivax HB®) given in a 3-dose schedule at 0, 1, and 6 months or 2 doses of 20 mcg/mL (Engerix-B®) administered simultaneously as a 4-dose schedule at 0, 1, 2, and 6 months [10].

Seroconversion to hepatitis B vaccine can occur in cancer patients with similar frequency to healthy subjects unless it is administered during chemotherapy [1, 3, 35]. Concomitant myeloablative regimens were associated with poor immune responses (nearly 20%) [1, 3, 36–38].

Tetanus, Diphtheria, and Acellular Pertussis Vaccination

Many cancer patients receiving chemotherapy are not protected against tetanus, diphtheria, and pertussis. Tetanus and diphtheria (Td) booster doses should be considered for oncology patients. For people ≥ 11 years of age who have not received tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine, or with unknown vaccination status, a dose of Tdap should be given and followed by tetanus and diphtheria toxoid (Td) booster doses every 10 years [6, 39, 40]. If possible, Tdap should be given before initiation of treatment. Even though data on immune response to tetanus and diphtheria vaccines are limited in this patient group, existing data on children receiving maintenance chemotherapy revealed a similar response as compared to healthy controls [40]. Adults with unknown or incomplete history of receiving 3-dose primary vaccination series should begin or complete the primary vaccination series including a Tdap dose. For unvaccinated adults, the first 2 doses should be given at least 4 weeks apart followed by the third dose 6–12 months later. For patients who have received incomplete vaccination (fewer than 3 doses), the remaining doses should be given [10].

Meningococcal Vaccination

For meningococcal vaccination, no specific recommendations can be made for cancer patients. Current guidelines on recommended immunization schedules should be followed [10]. Immune response to meningococcal vaccine may be suboptimal in oncology patients [6, 9, 10].

Human Papillomavirus (HPV) Vaccination

Patients with cancer should receive human papillomavirus (HPV) vaccine with the same indications and schedule as stated in the current guidelines [10]. For use in females, bivalent (2vHPV), quadrivalent (4vHPV), and 9-valent (9vHPV) HPV vaccines are licensed; for use in males, 4vHPV and 9vHPV are available. In cancer patients, response to vaccination may be suboptimal [6, 41]. Since the vaccine should be administered by intramuscular injection, thrombocytopenic patients may have a risk of developing hematoma [6].

Poliovirus Vaccination

The incidence of poliovirus infection is low in the United States and Western Europe. Routine vaccination of adults ≥ 18 years of age who reside in the United States is not recommended since most adults are considered to be immune, and the risk of exposure to wild poliovirus is low. Nevertheless, revaccination with inactivated polio vaccine (IPV) is still recommended for transplant recipients and oncology patients, particularly for those at elevated risk of poliovirus exposure [1, 6] such as travelers to areas where poliomyelitis is endemic or epidemic, and laboratory staff with possible exposure to specimens that may contain poliovirus. Administration of poliovirus vaccine to adults at risk of infection is scheduled according to the previous vaccination history and the particular time

period required for protective immune response. For adults who have not been vaccinated and at risk of exposure to poliomyelitis, primary immunization with IPV scheduled in 3 doses is recommended. The first and second dose of IPV should be given 1–2 months apart, and the third dose needs to be administered 6–12 months (at least 6 months) after the second dose. If completion of this schedule is not possible because of the time required for protection is limited, alternative vaccination strategies can be used. If ≥8 weeks are available before protection is needed, IPV vaccination schedule in 3 doses can be completed by giving each dose at least 4 weeks apart. If only 4–8 weeks are available, 2 doses of IPV should be given at least 4 weeks apart. If less than 4 weeks are available, a single dose of IPV should be given, and the remaining doses must be completed later if the person is still at risk of infection. For adults who have previously received a primary series of 3 or more doses and are at increased risk of exposure to poliovirus, 1 dose of IPV should be given. If a primary series of vaccinations have not previously been completed, and increased risk of exposure to poliovirus is present, the remaining doses of IPV should be given [42].

Vaccination of Household Contacts of Immunocompromised Patients

Immunocompetent household members of immunocompromised patients can receive inactivated vaccines according to the recommended immunization schedules. They should be vaccinated annually with either inactivated influenza vaccine or live attenuated influenza vaccine. However, live attenuated influenza vaccine is only recommended to healthy, nonpregnant individuals aged between 2 and 49 years [7, 10]. Live attenuated influenza vaccine should not be administered to household contacts of patients with severe combined immune deficiency (SCID) or HSCT recipients within 2 months after transplant and/or with GVHD. If live attenuated influenza vaccine is administered to a household member of these high-risk patients, contact should be avoided for 7 days. Oral polio vaccine should not be administered to household contacts of immunocompromised patients [7].

Other live vaccines—such as combined MMR vaccines, varicella vaccine, zoster vaccine, rotavirus vaccine (in infants aged between 2 and 7 months), yellow fever vaccine, and oral typhoid vaccine (as travel advice)—can be administered to healthy household members of immunocompromised patients. But, highly immunocompromised individuals should be advised to avoid handling of diapers of infants within 4 weeks of rotavirus vaccination. They should also avoid contact with any varicella or zoster vaccine recipient who experiences rash or skin lesions after vaccination. Contact should be avoided until the lesions are crusted [7].

Conclusion

Vaccination is of utmost importance for immunosuppressed patients for protection from several vaccine-preventable diseases. Patients with solid tumors can be safely vaccinated with non-live vaccines. Particular emphasis should be put on annual influenza vaccination and pneumococcal vaccination schedules—both of which can be applied as in healthy individuals. Since the morbidity and mortality from the latter diseases will be significantly higher in the immunosuppressed—thus in patients with solid tumors—the patient should strongly be advised to be vaccinated. The timing of vaccination is very important to achieve a protective immunity, and a timeframe when the patient is least immunosuppressed should be chosen when applying vaccines.

References

1. Decker W, Safdar A. Prophylactic vaccination of cancer patients and hematopoietic stem cell transplant recipients. In: Safdar A, editor. Principles and practice of cancer infectious diseases, current clinical oncology. Totowa: Humana Press, Springer Science+Business Media, LLC; 2011. p. 561–71.
2. Burroughs M, Moscona A. Immunization of pediatric solid organ transplant candidates and recipients. Clin Infect Dis. 2000;30:857–69.
3. Sommer AL, Wachel BK, Smith JA. Evaluation of vaccine dosing in patients with solid tumors receiving myelosuppressive chemotherapy. J Oncol Pharm Pract. 2006;12:143–54.
4. Cohen JI. Strategies for herpes zoster vaccination of immunocompromised patients. J Infect Dis. 2008;197(Suppl 2):S237–41.
5. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. Lancet Infect Dis. 2009;9:493–504.
6. Hibberd PL. Immunizations in patients with cancer. http://www.uptodate.com/contents/immunizations-in-patients-with-cancer. Accessed 31 Jan 2018.
7. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I, Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:309–18.
8. Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Koné-Paut I, Fasth A, Minden K, Ravelli A, Abinun M, Pileggi GS, Borte M, Wulffraat NM, EULAR. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis. 2011;70:1704–12.
9. National Center for Immunization and Respiratory Diseases. General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60:1–64. Erratum in: MMWR Recomm Rep 2011; 60: 993.
10. Kim DK, Bridges CB, Harriman KH, Advisory Committee on Immunization Practices (ACIP), ACIP Adult Immunization Work Group. Advisory Committee on Immunization Practices Recommended Immunization Schedule for adults aged 19 years or older - United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65:88–90.

11. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. Am J Med. 1997;102:2–9. discussion 25-6.
12. Elting LS, Whimbey E, Lo W, Couch R, Andreeff M, Bodey GP. Epidemiology of influenza A virus infection in patients with acute or chronic leukemia. Support Care Cancer. 1995;3:198–202.
13. Ljungman P. Respiratory virus infections in stem cell transplant patients: the European experience. Biol Blood Marrow Transplant. 2001;7(Suppl):5S–7S.
14. Ljungman P. Respiratory virus infections in bone marrow transplant recipients: the European perspective. Am J Med. 1997;102:44–7.
15. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis. 2004;39:1300–6.
16. Gribabis DA, Panayiotidis P, Boussiotis VA, Hannoun C, Pangalis GA. Influenza virus vaccine in B-cell chronic lymphocytic leukaemia patients. Acta Haematol. 1994;91:115–8.
17. Anderson H, Petrie K, Berrisford C, Charlett A, Thatcher N, Zambon AM. Seroconversion after influenza vaccination in patients with lung cancer. Br J Cancer. 1999;80:219–20.
18. Brydak LB, Całbecka M. Immunogenicity of influenza vaccine in patients with hemato-oncological disorders. Leuk Lymphoma. 1999;32:369–74.
19. Beck CR, BC MK, Hashim AB, Harris RC, University of Nottingham Influenza and the ImmunoCompromised (UNIIC) Study Group, Nguyen-Van-Tam JS. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis by etiology. J Infect Dis. 2012;206:1250–9.
20. Brydak LB, Guzy J, Starzyk J, Machała M, Góźdź SS. Humoral immune response after vaccination against influenza in patients with breast cancer. Support Care Cancer. 2001;9:65–8.
21. Ganz PA, Shanley JD, Cherry JD. Responses of patients with neoplastic diseases to influenza virus vaccine. Cancer. 1978;42:2244–7.
22. Nordøy T, Aaberge IS, Husebekk A, Samdal HH, Steinert S, Melby H, Kolstad A. Cancer patients undergoing chemotherapy show adequate serological response to vaccinations against influenza virus and *Streptococcus pneumoniae*. Med Oncol. 2002;19:71–8.
23. Ortbals DW, Liebhaber H, Presant CA, Van Amburg AL 3rd, Lee JY. Influenza immunization of adult patients with malignant diseases. Ann Intern Med. 1977;87:552–7.
24. Molrine DC, George S, Tarbell N, Mauch P, Diller L, Neuberg D, Shamberger RC, Anderson EL, Phillips NR, Kinsella K, Ambrosino DM. Antibody responses to polysaccharide and polysaccharide-conjugate vaccines after treatment of Hodgkin disease. Ann Intern Med. 1995;123:828–34.
25. Robertson JD, Nagesh K, Jowitt SN, Dougal M, Anderson H, Mutton K, Zambon M, Scarffe JH. Immunogenicity of vaccination against influenza, Streptococcus pneumoniae and *Haemophilus influenzae* type B in patients with multiple myeloma. Br J Cancer. 2000;82:1261–5.
26. Levine AM, Overturf GD, Field RF, Holdorf D, Paganini-Hill A, Feinstein DI. Use and efficacy of pneumococcal vaccine in patients with Hodgkin disease. Blood. 1979;54:1171–5.
27. Hartkamp A, Mulder AH, Rijkers GT, van Velzen-Blad H, Biesma DH. Antibody responses to pneumococcal and haemophilus vaccinations in patients with B-cell chronic lymphocytic leukaemia. Vaccine. 2001;19:1671–7.
28. Siber GR, Weitzman SA, Aisenberg AC. Antibody response of patients with Hodgkin's disease to protein and polysaccharide antigens. Rev Infect Dis. 1981;3(Suppl):S144–59.
29. Siber GR, Gorham C, Martin P, Corkery JC, Schiffman G. Antibody response to pretreatment immunization and post-treatment boosting with bacterial polysaccharide vaccines in patients with Hodgkin's disease. Ann Intern Med. 1986;104:467–75.
30. Feldman S, Gigliotti F, Shenep JL, Roberson PK, Lott L. Risk of *Haemophilus influenzae* type b disease in children with cancer and response of immunocompromised leukemic children to a conjugate vaccine. J Infect Dis. 1990;161:926–31.
31. Ek T, Mellander L, Hahn-Zoric M, Abrahamsson J. Intensive treatment for childhood acute lymphoblastic leukemia reduces immune responses to diphtheria, tetanus, and *Haemophilus influenzae* type b. J Pediatr Hematol Oncol. 2004;26:727–34.
32. Rusthoven JJ, Ahlgren P, Elhakim T, Pinfold P, Reid J, Stewart L, Feld R. Varicella-zoster infection in adult cancer patients. A population study. Arch Intern Med. 1988;148:1561–6.
33. Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. JAMA. 1992;267:1237–41.
34. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, Douglas JM Jr, Janssen RS, Ward JW, Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2006;55(RR-16):1–33. quiz CE1-4.
35. Hovi L, Valle M, Siimes MA, Jalanko H, Saarinen UM. Impaired response to hepatitis B vaccine in children receiving anticancer chemotherapy. Pediatr Infect Dis J. 1995;14:931–5.
36. Goyal S, Pai SK, Kelkar R, Advani SH. Hepatitis B vaccination in acute lymphoblastic leukemia. Leuk Res. 1998;22:193–5.
37. Rosen HR, Stierer M, Wolf HM, Eibl MM. Impaired primary antibody responses after vaccination against hepatitis B in patients with breast cancer. Breast Cancer Res Treat. 1992;23:233–40.
38. Weitberg AB, Weitzman SA, Watkins E, Hinkle C, O'Rourke S, Dienstag JL. Immunogenicity of hepatitis B vaccine in oncology patients receiving chemotherapy. J Clin Oncol. 1985;3:718–22.
39. Hamarström V, Pauksen K, Svensson H, Oberg G, Paul C, Ljungman P. Tetanus immunity in patients with hematological malignancies. Support Care Cancer. 1998;6:469–72.
40. van der Does-van den Berg A, Hermans J, Nagel J, van Steenis G. Immunity to diphtheria, pertussis, tetanus, and poliomyelitis in children with acute lymphocytic leukemia after cessation of chemotherapy. Pediatrics. 1981;67:222–9.
41. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER, Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56(RR-2):1–24.
42. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/polio.pdf. Accessed 31 Jan 2018.

Symptom Management in Gastrointestinal Cancers

38

Tugba Yavuzsen, Nazli Kazaz, Özgür Tanriverdi, Tulay Akman, and Mellar P. Davis

Introduction

Gastrointestinal (GI) cancer is a term for a group of cancers that includes cancers of the esophagus, gallbladder, liver, pancreas, stomach, small bowel (large intestine or colon and rectum) intestine, and anus.

Symptom management for GI cancers depends on the type of cancer, the stage, the development of systemic symptoms such as anorexia, early satiety nausea, dysgeusia and smell changes, and other comorbidities. In 2018, there were an estimated 1.7 million new cancers expected to be diagnosed and 609,640 cancer deaths in the United States, according to the American Cancer Society [1]. In the United States, colorectal cancer is one of the four most prevalent cancers by age and sex [1]. Patients diagnosed with cancer are confronted with many distressing symptoms. Fatigue is the most common symptom followed by pain, poor well-being, sleep disturbances, poor appetite, drowsiness, anxiety, depression, dyspnea, and nausea [2]. Symptoms may occur early, particularly in esophageal, gastric, and pancreatic cancers. Clinicians should assess a patient's symptom burden at the time of diagnosis using validated questionnaires. Symptoms may be directly related to the tumor or release of inflammatory cytokines or can result from treatment or associated comorbidities such as diabetes or cirrhosis.

Symptoms appear to cluster together in more than a random fashion and thus were used to define various syndromes in the early years of medicine [3]. Some of the clusters are defined clinically and some statistically. Symptom clusters may help in cancer diagnosis, management, and prognostication [4]. Certain symptoms negatively affect quality of life (QOL) and influence the treatment compliance of patients as well as add to their caregivers' burden. Assessing evolving symptom clusters with follow-up and early palliative intervention for symptoms can improve QOL for a cancer patient [5].

The philosophy of palliative care is based on interdisciplinary management—an approach that requires multiple specialties to work together, focused on the patient, family, and community at large. Providing for the palliative needs of the patient, wherever the patient is (at home, at nursing home, or in hospital), is the most basic cancer care. The palliative care philosophy treats death as a natural part of living, and trying to improve quality of life is fundamental to the experience of cancer. Palliative care does not seek to hasten or delay death and is patient-centered and not disease-centered. It focuses on providing a patient with the best quality of life possible until the moment of death. Palliative care should not be limited to the last period of life but should be applied early in the course of incurable cancers and to continue beyond death to support the patient's family.

In this chapter, we will discuss the management of common symptoms in GI cancers, including anorexia, cachexia, nausea and vomiting, mucositis, diarrhea, malignant bowel obstruction, ascites, jaundice, and hepatic encephalopathy. We will also discuss cancer-related fatigue, hematological and neuropsychiatric symptoms, pain, and skin problems.

T. Yavuzsen (✉)
Department of Internal Medicine, Division of Medical Oncology, Dokuz Eylul University Faculty of Medicine, Balcova, Izmir, Turkey

N. Kazaz
Department of Medical Oncology, Karadeniz Technical University, Kanuni Training and Education Hospital, Trabzon, Turkey

Ö. Tanriverdi
Department of Medical Oncology, Mugla Sitki Kocman University Faculty of Medicine, Menteşe, Mugla, Turkey

T. Akman
Department of Medical Oncology, Tepecik Education and Research Hospital, Izmir, Turkey

M. P. Davis
Lerner School of Medicine, Case Western Reserve University, Palliative Care Department, Geisinger Medical Center, Danville, PA, USA

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0_38

Nutritional Problems Associated with Gastrointestinal Cancer

At the cancer diagnosis, nutritional disorders become an emergent issue. Patients with cancer are frequently at risk of malnutrition, not only because of physical and metabolic effects of the disease but also because of adverse effects of anticancer treatments, and nutritional intake changes associated with food consumption or/and malabsorption [6]. Malnutrition is the most frequent nutritional disorder in patients with GI cancer and is associated with anorexia-cachexia syndrome (ACS), worsening of prognosis, and shortened survival rate. Early diagnosis of nutritional problems in GI cancer patients is essential to avoid further complications and improve survival rate. The greatest challenge in patients with GI cancer is to prevent involuntary weight loss, which is common in clinical practice and should be considered a warning sign in cachexia development. Early nutritional screening has been recommended in all patients to identify any specific risk of malnutrition [7].

Anorexia-cachexia syndrome can be missed with the initial diagnosis. Early assessment and diagnosis seems to be crucial for therapy [8, 9]. The prevalence of ACS in patients with advanced cancer, except with breast cancer, ranges from 25% to more than 80% before death [10].

Cachexia is a complex metabolic syndrome associated with underlying chronic disease, and is characterized by the loss of muscle with or without fat mass. It is characterized by systemic inflammation, negative protein and energy balance, and an involuntary loss of lean body mass with or without wasting of adipose tissue [9]. The pro-inflammatory cytokines produced by tumor cells is the main initiator that results in proteasome-dependent proteolysis and heat shock proteins upregulation as contributors to wasting [11]. In a study by DeWys in 1980, within Eastern Cooperative Oncology Group (ECOG) chemotherapy trials, weight loss was identified with high prevalence in cancer and it was associated with decreased survival [12].

Cachexia is responsible for 22% of all cancer deaths [13]. Anorexia (loss of appetite) affects up to three-fourths of cancer patients. Anorexia may not always accompany cachexia but these two symptoms often occur together in cancer.

The pathogenesis of human cancer anorexia is multifactorial but poorly understood. It likely results from altered peripheral hypothalamic signals and neurohormonal mediators due to up-regulated cytokines and eicosanoids and dysregulated of monoamines [14]. Multiple gastrointestinal symptoms were present simultaneously (causing anorexia) in 97% of advanced cancer patients [15]. Systematic assessment of these symptom profiles should help improve the understanding of pathophysiology and clinical features of ACS. The diagnosis of cancer-related anorexia is based on loss of appetite and the desire to eat. It is only a part of ACS and is usually associated with other gastrointestinal symptoms. Many questionnaires that have been developed provide a multidimensional assessment. However, it is often difficult to repetitively use these surveys due to the question burden on patients and their caregivers [16]. Therefore, there is a need for a simple, one-question survey for advanced cancer patients [17].

Cancer cachexia remains under-diagnosed and under-treated because of the lack of a universal definition; globally accepted diagnostic and classification criteria have not been established [18–21]. In a systematic review published in 2012 that looked at the value of symptom assessment to predict survival in advanced cancer patients [21], anorexia, cachexia, and weight loss were the most frequent symptoms in multivariate analyses to have prognostic significance—especially in advanced lung and GI cancers. The refractory cachexia is mostly seen in the terminal stages of cancer and is not reversible by aggressive nutritional support. However, pre-cachexia is important because early interventions with various medical treatments may prevent advancement to irreversible cachexia.

A significant proportion of patients will have sarcopenic obesity, which is often overlooked. Sarcopenic obese patients with cancer have an observed higher risk of dose-limiting toxicity during chemotherapy and surgery complications compared to non-sarcopenic obese patients [22, 23].

Professional nutritional counseling is a dedicated and repeated communication process that aims to provide patients with a thorough understanding of nutritional topics that can lead to lasting changes in eating habits. The best way to maintain or increase energy and protein intake is to be done with normal food. However, this is often difficult and, in addition to counseling, oral nutritional supplements (ONS) are required. It can be given to cancer patients through enteral tubes (enteral nutrition [EN]) or parenteral infusions (parenteral nutrition [PN]). A mini-review showed that there was no difference in improving the clinical outcomes except that PN resulted in more infections when compared with EN [24]. Physical therapy including physical activities of daily life, resistance and aerobic exercise training, and techniques also increase muscle mass and/or muscle strength.

Nausea and Vomiting in Gastrointestinal Cancers

Nausea is defined as an unpleasant subjective feeling with a need to vomit. Salivation, skin pallor, cold sweat, and tachycardia often accompany nausea. Vomiting is the retropulsion of gastric ingredients through the mouth. Approximately 50% of cancer patients will have nausea or vomiting during the course of their disease [25].

Nausea is regulated by the autonomic nervous system, but vomiting is controlled by the brainstem with a multistep reflex pathway. Vomiting occurs by way of afferent stimulation from the chemoreceptor trigger zone (CTZ, area postrema), cerebral cortex, limbic system, vestibular-labyrinthine apparatus, vagal afferent fibers in gastrointestinal tracts to the vomiting center, which is located in the medulla (nucleus tractus solitarius). Efferent impulses arise from the vomiting center to the salivation center, abdominal muscles, respiratory center, and cranial nerves [26]. There are multiple neurotransmitters and receptors (i.e., serotonin, dopamine, substance P) in the gastrointestinal tract, the vomiting center, and the CTZ that generate vomiting. Chemotherapeutic agents activate these receptors via vagus serotonin receptors (5HT3) and neurokinin 1 receptors (and substance P), which accounts for acute and delayed chemotherapy-induced nausea and vomiting (CINV), respectively [27].

The etiology-based classification and treatment (except CINV) is summarized in Table 38.1 [28]. The treatment strategies and agents vary according to the causes of nausea and vomiting (N&V). Cancer patients are exposed to many drugs during their treatment, and nausea is an important side effect of many anticancer drugs as well as the opioids used to control pain [29].

The other significant problem faced by cancer patients involves gastric motility disorders. Gastroparesis and loss of gastric accommodation have been described as complications of several GI malignancies and as a distant (paraneoplastic) effect from non-GI cancers such as lung cancer. These gastric motility disorders often accompany nausea and vomiting, abdominal pain, bloating, and early satiety [30, 31]. The prevalence of malignancy-associated gastroparesis is unknown but is probably under-recognized and undertreated [30]. In a prospective study, gastroparesis was related to impaired gastric emptying (tumor itself, ascites, hepatomegaly, drug-related, other) in 44% of patients, chemically caused (metabolic, drug-related, infectious) in 33%, visceral/serosal (bowel obstruction, other) in 31%, intracranial in 8%, and anxiety in 7% [32].

GI cancers may cause mechanical small bowel obstruction because of intrinsic or extrinsic compression. Surgery is unlikely to be helpful in most cases with gross cancer noted on abdominal cross-sectional imaging; therefore, palliative approaches should be utilized in an evidence-based manner. Gastrointestinal decompression is important in the treatment of nausea and vomiting from bowel obstruction (Table 38.1 shows other causes for nausea and vomiting [28]). Octreotide, hyoscine butylbromide, glycopyrrolate, ranitidine, corticosteroids, and antiemetics are helpful in reducing nausea and vomiting from bowel obstruction. Placement of stents and percutaneous gastrostomies can often relieve nausea and vomiting unresponsive to medication.

Nausea and vomiting are common side effects of chemotherapy and targeted agents for which patients with advanced GI cancers are treated [14]. Guidelines are only based on the type of chemotherapy agent used and its emetogenic potential. However, severity and duration of nausea and vomiting varies based on patient-related, tumor-related, and treatment-related factors [33]. Tumor location, type of chemotherapy agents used, and concomitant radiation exposure are responsible for variations in the incidence of nausea and vomiting [34, 35]. For example, cisplatin-induced nausea and vomiting is less likely to occur in patients with a history of chronic high intake of alcohol [36]. Female gender and patients younger than 50 years of age have a greater risk for nausea and vomiting on highly emetogenic and moderately emetogenic chemotherapy [37, 38]. History of motion sickness and emesis during pregnancy are the other risk factors.

Table 38.1 Etiology-based classification of nausea and vomiting [28]

Etiology	Examples	Appropriate first-line antiemetic and typical starting dose
Chemical	Drugs, e.g., opioids, digoxin, antibiotics, cytotoxic; toxins, e.g., ischemic bowel, infection; metabolic, e.g., hypercalcemia	Haloperidol, 1.5 mg bd or 5 mg subcutaneously over 24 h
Delayed gastric emptying	Drugs, e.g., opioids, tricyclic antidepressants; ascites Hepatomegaly; autonomic dysfunction	Metoclopramide, 10 mg qds or 40 mg subcutaneously over 24 h Domperidone, 10 mg qds
Gastrointestinal	Bowel obstruction	Hyoscine butylbromide, 60 mg subcutaneously over 24 h or cyclizine, 150 mg subcutaneously over 24 h Consider adding haloperidol and/or dexamethasone. If partial obstruction and/or abdominal colic consider metoclopramide instead
	Radiation colitis, post-chemotherapy	Ondansetron, 8 mg bd-tds
Cranial	Raised intracranial pressure, e.g., from tumor or intracranial bleed; meningeal infiltration	Cyclizine, 50 mg tds or 150 mg subcutaneously over 24 h (in conjunction with dexamethasone)
Vestibular	Drugs, e.g., opioids vestibular neuritis and labyrinthitis	Cyclizine, 50 mg tds or 150 mg subcutaneously over 24 h
Cortical	Anxiety, anticipatory N&V, pain	Benzodiazepines, e.g., oral lorazepam, 0.5 mg as required

bd twice daily, *tds* three times daily, *qds* four times daily, *e.g.* exempli gratia, *N&V* nausea and vomiting

Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced N&V has been classified as acute, delayed, anticipatory, breakthrough, refractory, and chronic [39–41]:

Acute and Delayed Nausea and Vomiting

Acute N&V occurs during the first 24 h after chemotherapy administration, whereas delayed emesis occurs more than 24 h after chemotherapy [42]. Acute emesis commonly begins within the first 2 h after chemotherapy administration, peaks in the first 4–6 h, and resolves within the first 24 h. Delayed N&V is associated with certain drugs (e.g., cisplatin, cyclophosphamide, doxorubicin, and ifosfamide) given at high doses or on sequential days. The etiologies and patient risk factors for acute and delayed N&V are similar. The incidence for both types of N&V varies by the emetogenic potential of the chemotherapeutic agents used [43–45]. Experiencing nausea and vomiting while receiving chemotherapy negatively affects patient quality of life; however, the incidence and severity of this complication is decreasing in recent years through the use of new antiemetic medications. Risk factors include:

- The emetogenic potential of the specific drug
- The dose
- The treatment schedule
- How chemotherapy agents are combined [46]

In a prospective study, patients with colon cancer on oxaliplatin-based chemotherapy received a 5-hydroxytryptamine 3 receptor antagonists (5 HT3RA) and dexamethasone 20 mg prior to oxaliplatin. Routine prophylaxis was not given for delayed emesis. The CR rate was 90% for acute emesis, but 54% for delayed emesis [43]. Recommendations now include the use of a neurokinin1 receptor antagonist (e.g., aprepitant or fosaprepitant) where available [47].

Anticipatory Nausea and Vomiting

Anticipatory N&V (ANV) is a learned or conditioned response. Anticipatory nausea occurs in one-third of patients receiving chemotherapy, while anticipatory vomiting occurs in about one in ten patients [48]. With cancer chemotherapy, the first chemotherapy infusion is part of a learning experience that provides information about the patient's particular susceptibility to nausea and vomiting. ANV occurs typically after three or four cycles of chemotherapy, largely after patients have experienced N&V with earlier treatments. Smells, sights, and sounds of the treatment room stimulate ANV. Many variables potentially affect the incidence of ANV. These risk factors are similar to those of CINV [49].

Aggressive prophylaxis with the initial courses of highly emetogenic and moderately emetogenic chemotherapy is the best way to avoid ANV. The proper use of antiemetics during chemotherapy may have a dramatic effect in decreasing the incidence of ANV [49]. In randomized trials, benzodiazepines combined with standard antiemetic therapy reduced the incidence of acute and ANV significantly. Guidelines also recommend lorazepam and alprazolam combined with antiemetics [50–52]. Behavioral therapies (relaxation/systematic desensitization, hypnosis with guided imagery, music therapy) and acupuncture/acupressure also can be helpful and are recommended for ANV [53–56].

Breakthrough Nausea and Vomiting

Breakthrough N&V describes patients who fail on antiemetic prophylaxis during initial chemotherapy cycles within 5 days (≥3 episodes of vomiting).

Refractory Nausea and Vomiting

Patients who have refractory N&V show no response to antiemetic treatment.

Chronic Nausea and Vomiting

Chronic N&V has a variety of potential etiologies. Potential factors include gastrointestinal, cranial, metabolic, drug-induced (e.g., morphine), cytotoxic chemotherapy-induced, and radiation-induced mechanisms [42].

The American Society of Clinical Oncology (ASCO) has developed a rating system for chemotherapeutic agents and their respective risk of acute and delayed emesis (Table 38.2)

Table 38.2 Emetogenic potential of intravenous and oral antineoplastic agents used in GI cancers [57]

Degree of emetogenicity (incidence)	Agent
High (>90%)	Cisplatin
Moderate (30–90%)	Oxaliplatin
	Carboplatin
	Epirubicin
	Irinotecan
	Imatinib
Low (10–30%)	Paclitaxel
	Docetaxel
	Mitomycin
	Gemcitabine
	5-Fluorouracil
	Etoposide
	Capecitabine
	Tegafur/uracil
	Cetuximab
	Trastuzumab
	Panitumumab
	Ramucirumab
	Regorafenib
	Sunitinib
	Everolimus
	Ziv-aflibercept
Minimal (<10%)	Bevacizumab

[57]. Chemotherapy drugs are located in all four groups commonly used in GI cancers. ASCO guidelines largely use the chemotherapy agent to grade the risk of N&V [57].

Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting

Highly Emetogenic Chemotherapy

The Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) have each created CINV management guidelines. All three guidelines [58] suggest a combination of 5 HT3RA, dexamethasone, and neurokinin-1 receptor antagonist (NK1 RA) on the first day for acute CINV, and NK1 RA with dexamethasone prophylaxis is recommended for delayed CINV for highly emetogenic agents. The NCCN guidelines recommend netupitant/palonosetron and dexamethasone combination for acute CINV and olanzapine for both acute and delayed emesis (in combination with palonosetron and dexamethasone for acute emesis prophylaxis).

Moderately Emetogenic Chemotherapy

Combinations of 5HT3RA and dexamethasone with or without NK1 RA are recommended for acute emesis with moderately emetogenic chemotherapy. Triple antiemetics are recommended the MASCC/ASCO guidelines for anthracycline and cyclophosphamide chemotherapy. NCCN guidelines recommend triple prophylaxis for the other moderately emetogenic agents (e.g., carboplatin, epirubicin, ifosfamide, and irinotecan) additionally and also recommend netupitant/palonosetron and dexamethasone combination. The use of olanzapine is recommended by the NCCN for the high emetogenic group. For delayed emesis, dexamethasone is the preferred agent; 5HT3RA can be used alternatively instead of dexamethasone. Metoclopramide is not recommended in the new guidelines for moderately emetogenic chemotherapy. Olanzapine is superior to metoclopramide in treating breakthrough nausea and vomiting.

Low Emetogenic Chemotherapy

Steroid alone is recommended with low emetogenic chemotherapy for prophylaxis of acute emesis. The NCCN guidelines recommend prochlorperazine or metoclopramide for prevention of acute emesis as an alternative to steroid or 5HT3RAs. There is no recommendation for delayed emesis.

Minimal Emetogenic Chemotherapy

No prophylaxis is suggested routinely before minimal emetogenic chemotherapy, according to all three guidelines.

Management of Breakthrough and Refractory Nausea and Vomiting

Dopamine receptor antagonists (metoclopramide), benzodiazepines (lorazepam), and neuroleptics (olanzapine) are suggested by the MASCC and NCCN guidelines for management of breakthrough and refractory N&V.

Non-pharmacological Strategies

Non-pharmacological strategies may help to reduce nausea and vomiting and may help the treatment with drugs. These strategies include nutritional advice (avoiding strong smells and foods that taste spicy or salty, taking frequent but small meals), acupuncture and acupressure (effective in postoperative N&V and CINV), relaxation methods, and behavior therapy [59].

Mucositis, Diarrhea, and Dysphagia

Mucositis and diarrhea are common toxicities caused by systemic chemotherapy, targeted agents, or radiation therapy, which share a common mechanism [60, 61]. Mucositis is a mucosal damage caused by an inflammatory response to treatment. Stomatitis or oral mucositis chronologically occurs later than small bowel mucosal damage. Diarrhea may occur as a result of increased motility or ion secretion in the absence of mucosal damage. The prevalence of mucositis is 20–40% of patients receiving standard-dose chemotherapy and 80% receiving high-dose chemotherapy [62]. The prevalence of oral mucositis in colorectal cancer patients on chemotherapy varies from 42% to 21% [61]. The clinical effects of mucositis on patients depend on anatomical site. Painful ulceration and dysphagia reflect upper gastrointestinal toxicity while abdominal cramps, bloating, and diarrhea reflect small bowel and colon toxicity [63]. The pathogenesis is complex and consists of five stages as proposed by Sonic et al.: (1) initiation, (2) upregulation and message generation, (3) signaling and amplification, (4) ulceration, and (5) healing phase [64].

Irinotecan and 5-fluorouracil (5-FU), often used in combination chemotherapy regimens for GI cancers, have been extensively researched [61]. The most common side effect is diarrhea in patients receiving adjuvant 5-FU-based chemotherapy regimens. Gastrointestinal toxicity is influenced by type of doses—bolus or infusion 5-FU—and time of day (there is less toxicity at night due to slower cellular division at night along the mucosa), patient genotype for metabolizing enzymes (5-FU) and cytochrome P450 (CYP1A1 for irinotecan), and comorbidities [65, 66]. Monoclonal antibodies to epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, used to treat advanced colorectal cancer are known to cause diarrhea too [60]. Bevacizumab and other monoclonal antibodies used against vascular epidermal

growth factor (VEGF) cause less diarrhea than other multi-targeted tyrosine kinase inhibitors (TKIs) directed at VEGF receptors [67]. In a study of 747 patients who received TKIs, the most common reported GI side effect was oral mucosal sensitivity (dysesthesia) [67]. Regorafenib, an oral small TKI, which has been used increasingly in the treatment of metastatic colorectal cancer, is also known to produce mucositis [68]. Few evidence-based treatments are available and no licensed agent is available for prophylaxis. Dose modification is usually done with additional cycles once mucositis occurs.

Published interventions for mucositis (not including the oral cavity) are amifostine, octreotide, sucralfate enemas, sulfasalazine, and probiotics, which should be given as per guideline recommendations. For oral mucositis, basic oral care is the main treatment. In addition, growth factor and cytokines, anti-inflammatories, antimicrobials, coating agents, patient-controlled analgesia, laser and light therapy, cryotherapy, and natural and miscellaneous agents have been reported to be helpful [69].

Carcinoid tumors arise from neuroendocrine cells, which are widespread in the human body, especially in the organs derived from the primitive intestine. One-third of those occur in the GI tract. Malignant carcinoid syndrome is characterized by an array of signs and symptoms, such as hot, red flushing of the face; debilitating diarrhea; and asthma attacks caused by vasoactive hormones secreted by metastases from carcinoid tumors [70]. Intestinal obstruction may result from the primary tumor or from the sclerosing reaction in the surrounding mesentery. Patients with severe diarrhea should be careful to avoid dehydration or vitamin deficiency. Systemic therapy should be used to control humorally mediated symptoms when the tumor spreads elsewhere. The somatostatin analogs octreotide and lanreotide are used to control carcinoid symptoms and tumor progression in advanced inoperable disease [71]. Telotristat-ethyl, which is a tryptophan hydroxylase inhibitor, should be considered in addition to somatostatin analog (SSA) therapy for diarrhea not controlled by SSA [72]. Anti-proliferative drugs may be useful for symptom palliation. Antineoplastic agents inhibit cell growth and proliferation, and interferons show antiviral, antitumor, and immunomodulatory actions for the management of carcinoid syndrome [73].

Esophageal cancer and treatment-related stricture may cause progressive dysphagia, nutritional problems, and weight loss. Nutritional assessment should be carefully monitored for this patient population to avoid ACS. More than 50% of patients already have inoperable disease at the time of diagnosis [74]. When looking at the outcomes of patients with advanced esophageal cancer who receive palliative care by either stent alone or stent plus an additional modality, the combined modality showed significant improvement in overall survival rates as well as QOL scores [74]. A meta-analysis and systematic review emphasizing the complications of stent placement in patients with esophageal cancer has shown that some stents, thermal ablative therapy, and brachytherapy have been associated with fewer complications [75].

Malignant Bowel Obstruction in Gastrointestinal Cancers

Malignant bowel obstruction (MBO) is not an infrequent complication in patients with advanced GI cancer. It is most commonly seen in advanced colon cancer (25–40%), followed by gastric cancer (6–19%) [76, 77]. Small bowel obstruction occurs more frequently than the large bowel obstruction (61% versus 33%) [78].

The diagnostic criteria of MBO are:

- Clinical evidence of bowel obstruction that is manifested by nausea, vomiting, and colic and abdominal pain
- Radiographic or endoscopic evidence of obstruction distal to the Treitz ligament
- The presence of primary intra-abdominal with incurable disease based on computed tomography (CT) or magnetic resonance imaging (MRI)
- Extra-abdominal primary cancer with clear intraperitoneal metastases [79]

Pathophysiological mechanisms responsible for obstruction include mechanical obstruction (such as intrinsic tumor growth within bowel lumen or extrinsic compression from outside the cavity, benign adhesions, post-irradiation fibrosis, intussusception) and motility disorders (tumor infiltration of mesentery, bowel muscle, celiac, or hypogastric plexus). The pathophysiology involves accumulation of gastrointestinal secretion proximal to the obstruction, decreased gastrointestinal absorption, hyper- or hypomotility, and inflammation. Constipating drugs (e.g., anticholinergic, opioid), paraneoplastic neuropathy, or pseudo-obstruction may contribute to the development of MBO [80]. Often more than one factor is responsible for obstructions.

Nausea, vomiting, colicky abdominal pain, and constipation are the symptoms of MBO. Nausea presents early and is severe in upper MBO. Vomiting can be constant or episodic and contain aqueous, mucous, or bilious secretions. Often vomiting relieves the nausea only to have nausea recur a few hours later. In lower obstruction, vomiting may be infrequent and nausea less severe. The colic pain is caused by peristalsis with increased endoluminal pressure in the absence of effective transit. Borborygmi are often heard when auscultating the abdomen. Pain is periumbilical and not well localized. Tumor infiltration of abdominal structures or peritoneum is responsible for the continuous pain [80]. MBO also may be accompanied by anemia (70%), hypoalbuminemia (68%),

changes in hepatic enzymes (62%), dehydration and prerenal renal azotemia (44%), cachexia (22%), ascites (41%), palpable abdominal tumor masses (21%), periumbilical nodes (called Sister Mary Joseph nodes), a Blumer shelf on rectal examination, and cognitive impairment from metabolic disturbances (23%) [81].

Management requires a multidisciplinary involvement and multimodal therapy. If estimated life expectancy is months and the patient is a candidate for surgery (no gross disease on CT scan, normal albumin, nutritionally fit, and with chemotherapy treatment options), surgery is the treatment of choice. Surgery may be avoided in patients with multiple comorbidities, poor nutritional status, history of radiotherapy to the abdomen or pelvis, level of obstruction or multiple obstructions, ascites, peritoneal carcinomatosis, palpable intra-abdominal masses, very advanced disease, poor performance status, and possibly advanced age [82, 83]. Surgical complications in bowel obstruction are common in those with advanced intra-abdominal carcinomatosis, diminishing QOL, and having a 30-day post-surgery mortality rate of 30%.

For poor-risk patients, pharmacological and interventional therapies may be beneficial by providing symptomatic relief. The pharmacological options include opioids, antiemetics (metoclopramide, haloperidol, or olanzapine), corticosteroids (dexamethasone), anticholinergics, octreotide, and combinations. Nausea and vomiting are the most distressing symptoms and may be relieved by combination of antiemetics and anti-secretory agents. Metoclopramide is the first choice in antiemetic drugs for partial but not complete bowel obstruction due to its prokinetic effects. If bowel function cannot be maintained, anti-secretory medications are recommended by the NCCN guidelines. Drugs available for the reduction of gastrointestinal secretions include scopolamine (hyoscine) butylbromide outside of the United States, glycopyrrolate within the United States, and octreotide, a somatostatin analog, within the United States and Europe.

The interventional therapies that may palliate nausea include a venting gastrostomy tube, percutaneous endoscopic gastrostomy tube, and endoscopic stents. Nutritional support is a very important part in the management of MBO if attempts are made to reverse the obstruction surgically. Some individuals with obstructions not amenable to surgery, with slow growing tumors and not cachectic, may benefit from parenteral nutrition and should be given a trial of nutritional support. Individuals with an expected short survival do not benefit from total parenteral nutrition. Total parenteral nutrition is recommended for patients with years to months to live based on NCCN guidelines. Hydration should be considered for those who are not candidates for nutritional support. Hypodermoclysis (subcutaneous infusion) of 1 L, but not more than 2 L, a day may improve symptoms and forestall cognitive failure from dehydration.

The prognosis of patients with MBO who have received maximal surgical, chemotherapeutic, and interventional treatment is very poor; survival ranges from a few weeks to a few months [84].

Malignant Ascites

Malignant ascites is a common occurrence with GI and pelvic cancers. The prevalence of malignant ascites in GI cancers is approximately 15% [85]. The pathophysiology seems to be complex and multifactorial. Abdominal fluid is absorbed through lymphatics on the inferior surface of the diaphragm, which become obstructed with peritoneal cancer altering the balance between production and absorption. Increased permeability of tumor vessels via vascular endothelial growth factor (VEGF), and macro and micro invasion of lymphatic channels underlie fluid accumulation [86]. Other mechanisms causing ascites are generally associated with peritoneal and liver metastasis leading to hypoalbuminemia and venous obstruction.

Treatment approaches in patients with ascites are mostly palliative, and do not impact survival. Common medical interventions include paracentesis and diuretics. There are no randomized controlled trials of diuretics in malignant ascites but anecdotally it can be successful in some patients [87]. Multiple paracentesis with indwelling catheters at regular intervals control symptoms such as dyspnea, nausea, and abdominal pain [88]. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of ascites has been reported to be successful in selected patients such as those with pseudomyxoma peritonei [89]. This procedure should be considered in carefully selected patients because of its morbidities. Other treatment approaches such as peritoneal-venous shunting procedures, targeted therapies, immunotherapy, anti-VEGF agents, and radioisotopes are promising, but further investigations are necessary [90].

Jaundice

Gastrointestinal cancers with liver metastases cause jaundice by obstructing intrahepatic or extrahepatic bile ducts [91, 92]. Jaundice portends a poor outcome, delays or disrupts antitumor treatment, and contributes to poor quality of life and mortality. Jaundice is classified as prehepatic, hepatic, and posthepatic obstruction. Prehepatic jaundice is caused by hematological and genetic disorders. Hepatic jaundice is a heterogeneous group of disorders associated with necrosis of hepatocytes (hepatocellular injury) or functional impairment of biliary excretion (cholestasis). Posthepatic jaundice develops tumor infiltration within extrahepatic bile ducts or

by compression from regional nodal involvement. History, physical examination, blood tests, and noninvasive imaging techniques are able to differentiate the various causes of jaundice. Relief of biliary obstruction may be by way of surgical or nonsurgical (metallic or plastic stents) decompression and provides relief from pruritus and jaundice [92]. Pruritus from a biliary obstruction may respond to oral naltrexone, bile acid binders, rifampin, ondansetron or selective serotonin reuptake inhibitors, or mirtazapine. Pruritus does not respond to gabapentinoids.

Fatigue in Gastrointestinal Cancers

Fatigue is one of the most distressing symptoms associated with cancer and cancer treatment, but as a symptom it is quite often underestimated. Cancer and its treatment both cause fatigue. The prevalence is 70–100% in different studies [93]. Fatigue occurs in half of the patients during chemotherapy and 60–93% patients during radiotherapy [94–96].

Cancer-related fatigue (CRF) is complex, and has psychological, physical, and emotional domains. CRF is defined as a persistent, subjective sense of tiredness related to cancer or cancer treatment. Fatigue may be seen in patients at any stage in the course of the illness but is more prevalent in patients with more advanced disease and those on active therapy. The etiology of fatigue is multifactorial in the majority of patients with advanced cancer. The most important factors contributing to CRF are progressive tumor growth, treatment with a wide range of systemic therapies, or radiation therapy. Also anemia, pain, dyspnea, nausea, emotional distress, cognitive impairment, sleep disturbance, anorexia, cachexia, and poor nutrition are the other important factors contributing to CRF [97]. Radiotherapy and chemotherapy commonly cause anemia, diarrhea, anorexia, nausea, vomiting, and weight loss and contribute to fatigue.

Fatigue associated with pain, sleep disturbance, or lack of appetite is common in GI cancer patients and significantly affects the overall quality of life [97, 98]. A prospective cohort study evaluated the effect of fatigue on overall survival in patients with esophageal cancer [99]. This study found that CRF was associated with a decreased survival. Anemia and poor nutrition frequently occur in GI cancer patients, and anemia is considered an important cause of fatigue. Malnutrition and weight loss independently affect fatigue and QOL in GI cancers [100]. Cognitive impairment is an important symptom in cancer patients related to side effects of treatments and/or cancer diagnosis. It is also well-known that fatigue and cognitive impairment often occur together. Vardy et al. published a large longitudinal study that evaluated cognitive function and fatigue in colorectal cancer patients [101]. Three groups of patients were compared before and after surgery, patients with limited metastatic disease, and healthy controls. They found that women with early stage of colorectal cancer had greater cognitive impairment and 52% of patients with early stage of colorectal cancer had self-reported fatigue.

Cancer-related fatigue profoundly affects QOL of both patients and their families, and as a result it decreases motivation [102] and may also significantly interfere with the delivery of effective therapy [93]. In managing fatigue, the possible underlying causes in a patient must be very carefully assessed. Questionnaires that examine the physical, emotional, and cognitive aspects of fatigue may be useful. Several tools are available: Brief Fatigue Inventory (BFI); Multidimensional Fatigue Inventory (MFI-20), which gauges dimensions of fatigue such as general fatigue, physical fatigue, decreased activeness, motivation and psychological fatigue [103]; the Rotterdam Symptom Checklist (RSCL) [104]; and the Functional Assessment of Cancer Therapy-Fatigue Scale (FACT-F) [105]. The intensity of fatigue can be examined by means of a verbal rating scale (VRS), visual analog scale (VAS), and numerical rating scale (NRS) of the linear analog scale assessment. Also, the possible underlying causes must be assessed.

Specific treatment to reverse the underlying causes such as treating anemia or metabolic or endocrine abnormalities, as well as managing pain, sleep disturbance, depression, or anxiety are initial treatments. Appropriate psychotherapy and physiotherapy, and dietary education must be given to the patient. Cognitive and behavioral therapy can be done individually. Regular exercise may decrease fatigue, depression, and anxiety symptoms [93].

Moreover, for patients with severe fatigue, in whom nonpharmacologic methods are not helpful, pharmacological treatment can be used. Corticosteroids decrease fatigue in cancer patients. Methylprednisolone at a dose of 32 mg/day reduces fatigue [106]. Megestrol acetate at a dose of 160–480 mg/day demonstrated rapid improvement in fatigue and can be used in the treatment of fatigue symptom [107]. Psychostimulants such as methylphenidate, dexmethylphenidate, or modafinil decrease fatigue and alleviate depression. Psychostimulants are found to be especially effective in treating fatigue related to opioid-induced sedation. Randomized trials of psychostimulants for fatigue have conflicting results. The potential benefit of psychostimulants for fatigue in advanced cancer patients has not been established. More research is needed to define the role of psychostimulants in the management of fatigue [108–110]. Some herbal remedies, such as ginseng, may help to reduce fatigue. A randomized, double-blind study of 364 patients from 40 cancer centers showed that American ginseng at 2 g per day for 8 weeks was effective in reducing CRF [111].

Non-pharmacologic interventions are also important for management of cancer-related fatigue. Physical activity, yoga, cognitive behavioral therapy, and educational interventions for patients and care providers are the most recommended [112, 113].

Hematological Complications

Hematological symptoms are common among patients with GI cancers, particularly gastric and pancreatic cancer. The symptoms generally relate to an increase or decrease in the number of blood cells, as well as disorders of the hemostatic system [114]. The symptoms can present at the time of diagnosis, during the process of treating the cancer, and during the follow-up period due to the cancer itself, its metastasis, and systemic treatment, including radiation therapy.

These issues can result from various causes. They may not only be related to cancer- or metastases-related issues, such as bone marrow infiltration, and paraneoplastic hematological syndromes, which are not associated with the primary tumor or its metastatic lesions [114]. Hematological complications also can result from cancer treatment, such as chemotherapy-induced cytopenias [114], including thrombocytopenia, anemia, and leukopenia as well as pancytopenia [115]. These can arise from myelosuppression because of chemotherapy, targeted molecular therapy, and radiation treatment [116].

Furthermore, many other medical problems—such as comorbidities, drugs interactions, adverse effects from medications other than anticancer-cancer drugs, as well as metabolic disorders—can be underlying causes of hematological symptoms.

Anemia, which can lead to weakness and fatigue, is the most common hematological disorder in patients with gastrointestinal cancer [114, 117]. It can often arise from iron deficiency, which relates to occult or massive bleeding via the gastrointestinal tract and other causes, such as gastrointestinal tract surgery, cancer cachexia, and nutritional disorders during the time of the diagnosis and the process of treating cancer [117, 118]. Similarly, another cause of anemia is vitamin B12 deficiency, which can be associated with gastrectomy surgery, gastric cancer related with chronic active gastritis called pernicious anemia, linitis plastica, adenocarcinoma of the small intestine, and neuroendocrine tumors localized in the stomach and small intestine [117]. Vitamin B12 deficiency leads to megaloblastic anemia with oval macrocytosis as well as neurocognitive symptoms such as walking and movement disorders, disturbed vision, depression, behavioral disorders, and a decline in mental abilities such as memory, understanding, and judgment [118]. In addition, a deficiency in folic acid level can result in macrocytic anemia [118].

Thrombocytopenia is often an adverse effect of anticancer drugs or bone marrow suppression because of direct cancer infiltration [114, 117, 119]. Many drugs have been reported to cause thrombotic microangiopathy [120, 121], including oxaliplatin, which is commonly used in the treatment of colorectal, gastric, and pancreatic cancers. Unlike lymphomas and other solid tumors, such as breast and lung carcinomas, GI cancers present less frequently with idiopathic thrombocytopenic purpura (ITP), as well as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC) [116, 122–125].

Deep vein thrombosis (DVT) and thromboembolism are not infrequent and occur mostly in patients with pancreatic and gastric cancers and may occur as the first presentation of malignancy [126, 127]. Moreover, DVT can be seen as a paraneoplastic syndrome called superficial migratory thrombophlebitis, particularly in patients with pancreatic carcinoma [127]. Several risk assessment tools have been developed for calculating the risk of thrombosis in cancer patients. Each tool is designed for a specific risk assessment. It is important to note that these tools should only be used in cancer patients who meet the criteria [128]. Current guidelines recommended low-molecular weight heparin (LMWH) monotherapy over vitamin K antagonist for the treatment of cancer-associated venous thromboembolism. However, recent clinical data could not show any superior efficacy for prevention and mortality rate [129]. The direct oral anticoagulants may be effective treatment, although the risk reduction for recurrent DVT with these agents compared to LMWH has not been well-assessed [130]. Many targeted agents are used in cancer treatments, but hematologic toxicity is seldom seen [131]. Nevertheless, bevacizumab, a monoclonal antibody-targeted VEGF, is an important cause of deep vein thrombosis in patients with colorectal carcinoma [132].

Neuropsychiatric Symptoms of Gastrointestinal Cancers

Neuropsychiatric symptoms are most commonly encountered in clinical situations among patients with cancer [133]. Not only can symptoms arise from various cancer- or metastases-related issues (e.g., brain metastases, leptomeningeal involvement, and spinal cord invasion), as well as paraneoplastic neurological syndromes not associated with the primary tumor or its metastatic lesions, but also cancer treatment-related issues [133, 134]. Furthermore, many other medical problems—such as comorbidities, side effects of medications apart from anticancer drugs, and metabolic disorders—also can be underlying causes of these symptoms [133]. However, neuropsychiatric symptoms are relatively uncommon among patients with GI cancers compared to those with other solid malignancies [133, 134]. Using the current literature, we review the neuropsychiatric symptoms in patients with GI cancers as follows.

Differential diagnosis is the first step in an approach to neuropsychiatric symptoms in GI cancer patients. Therefore, they must be carefully distinguished from intracranial

hemorrhage; ischemic cerebrovascular disease; otitis media; hypertensive attack; acute cardiac syndromes; diabetic neuropathy; vertebral mechanical diseases; metabolic disorders, such as drug intoxication, hypo- or hypernatremia, hypo- or hypercalcemia, uremic or hepatic encephalopathy, and hypoglycemia; and psychiatric diseases, such as psychosis, depression, and anxiety [133–135]. This is because the management of these symptoms caused by cancer or cancer treatment is very different from the approaches to treating other causes.

Cancer-Related Neurological Symptoms

Cancer-related neurological symptoms in patients with GI cancers include headache, vision disorders, dizziness, ataxia, diplopia, syncope, seizures, sensory or motor disorders, dysarthria, neuropathic pain, and delirium [133–135]. Headaches are the most common among all of these symptoms [133]. Brain metastases are the most important cause of cancer-related headaches, and they cause increased intracranial pressure and other neurological symptoms that may be often accompanied by a headache, depending on where the metastatic lesions are in the brain, their size, and number of masses [133, 134]. In studies, the incidence of brain metastasis ranged from 2% to 8%, which is very rare in comparison to the incidence among patients with breast and lung cancer [133–135]. However, this rate is increased in patients with colorectal cancer, which is due to longer survival on new targeted molecular therapies [135].

Ataxia is another important neurological symptom and it may be related to cerebellar metastasis from GI cancer, as well as paraneoplastic cerebellar degeneration. The differential diagnosis consists of metabolic disorders, peripheral vertigo, alcohol consumption, and drug interactions [134, 135]. Paraneoplastic neurological syndromes are seen rarely in patients with GI cancers. To the best of the authors' knowledge, based on a literature search, only a few case reports have identified paraneoplastic syndromes in patients with colorectal and gastric cancers [134, 135].

Treatment-Related Neurological Symptoms

Peripheral neuropathy is an important and commonly seen treatment-related symptom in patients with GI cancers, and it can result from an oxaliplatin- or taxane-based chemotherapy [133–136]. It occurs always as sensorimotor polyneuropathy in the hands and feet [134, 136]. It can be acutely prevented by prophylactic venlafaxine. Additionally, other cancer drugs that cause neuropathy include cisplatin, gemcitabine, irinotecan, 5-fluorouracil, and capecitabine [136]. The American Society of Clinical Oncology (ASCO) has released guidelines for the management of chemotherapy-induced peripheral neuropathy (CIPN) in oncology patients [137]. The use of some drugs, supplements, and vitamin E have been recommended for prevention and treatment. Multiple studies and meta-analyses have failed to identify any drug that can prevent CIPN. Duloxetine is the only drug that has demonstrated efficacy for the treatment of CIPN [137].

Cancer-Related Psychiatric Symptoms

Psychiatric symptoms in relation to cancer or its metastasis, as well as psychiatric paraneoplastic disorders, have not been defined well in the literature [138]. Regardless, most cancer patients suffer from psychiatric disorders, such as depression, anxiety, cognitive disruptions, and fear of death, during the time of cancer diagnosis and treatment, as well as during the follow-up period as a cancer survivor [138, 139].

Treatment-Related Psychiatric Symptoms

As with other cancer patients, patients with GI cancers suffer mostly from various cognitive and psychological disorders, such as depression, panic attacks, anxiety, fear of death, forgetfulness, and sleep disorders [138]. In previous studies, the prevalence of depression and anxiety in cancer patients ranged from 35% to 75% [138]. Decreases in cognitive function and in movement can lead to worsening of the psychologic status of patients, resulting in impaired mood and reduction in QOL [138, 140]. Although the underlying mechanism has not been defined clearly, the "chemo-brain" is an issue that should be discussed because it may lead to cognitive and emotional disorders [138, 141].

Delirium is another important symptom in cancer patients, which occurs in all stages of cancer, especially in the terminal stage [142]. Many issues can be suggested as causes of delirium in cancer patients, including infections, fever, and metabolic disorders, as well as the use of opioids and other drugs [142].

Neuropsychiatric symptoms in patients with GI cancers can present at the time of diagnosis, during the process of treating cancer, and during the follow-up period, except in the terminal stage, due to both the cancer itself and its metastasis and the systemic treatment, including radiation therapy. In conclusion, the effective and correct management of these symptoms is the most important for patients.

Pain in Gastrointestinal Cancers

Pain is one of the most common and distressing symptoms experienced by cancer patients. It is defined by the International Association for the Study of Pain as an

unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in relation to such damage [143]. According to a systematic review, the prevalence of pain is 59% of patients undergoing cancer treatment, 64% of patients with advanced disease, and 33% of patients after curative treatment [144]. In another study, which examined symptoms reported by patients after open-ended questioning vs. those systematically assessed using survey [145], pain was the most common symptom identified by open-ended questions but fatigue was more prevalent when systematic assessment was done. The European pain survey assessed 5084 adult cancer patients [146]. The prevalence of pain in all patients (excluding those patients with skin cancer) was 72%. The highest prevalence of pain was found in patients with pancreatic and colorectal cancers.

Cancer pain is a complex, temporally changing symptom of the mixed mechanisms. It involves inflammatory, neuropathic, ischemic, tumor-related compression, and invasion at multiple sites [147]. Interestingly only 1/3 of bone metastases are painful, indicating that local factors such as cytokines or hypoxemia are important contributors to pain. Cancer pain is a subjective symptom—a heterogeneous experience that is influenced by pain memory, gender, genetics, expectations, mood, and culture. The first step is diagnosis, and the second step is assessment. These are important for the management of pain. Cancer pain is categorized as acute and chronic based on onset and duration. Causes of pain are mostly from the underlying cancer or its metastasis and less often secondary to antineoplastic therapies and comorbidities unrelated to cancer [148]. Considering the complexity of the neurophysiological pain and neurochemical process, clinicians need to evaluate the pathophysiological mechanisms, etiologies history, and physical findings obtained as well as the need to integrate inspection and testing. According to the pathophysiology of cancer pain classified as nociceptive, neuropathic, idiopathic, and psychogenic, it is oftentimes a mixed disorder.

Cancer pain is relieved in 80–90% of patients using an opioid-based analgesic regimen and the World Health Organization's (WHO) analgesic ladder as guidelines [149, 150]. Morphine has long been accepted as the opioid choice for moderate to severe pain. Management of cancer pain also requires expertise in the use of non-opioid analgesics and other adjuvant analgesics such as glucocorticoids, tricyclic antidepressants, anticholinergics, and bisphosphonates.

Neuropathic pain management is difficult. The prevalence of neuropathic pain varies between 19% and 39% in patients with cancer [151, 152]. It has a higher negative impact on QOL than nociceptive pain. The use of only morphine is often insufficient to treat neuropathic pain, therefore adjuvant agents should be considered for pain management. Neuropathic pain is associated with cancer type, stages, or chemotherapy agents [152]. Some chemotherapy agents, such as oxaliplatin, cause neuropathic pain leading to neurotoxicity. Oxaliplatin is a commonly used third-generation platinum derivate that has been demonstrated to be effective in GI tumors, especially in colorectal cancer studies. Grade 3 sensory neurotoxicity induced by oxaliplatin has been observed in 12.4–18% of patients during the treatment phase [153, 154] and 2% of patients at 2 years following discontinuation [155].

Invasive methods can be used in case of failure of pharmacological treatment. The neurolytic blocks of sympathetic pathways, including celiac plexus block (CPB) and superior hypogastric plexus block (SHPB), have been used for years. The European Palliative Care Research Collaborative group [156] has published a systematic review along with its recommendations for sympathetic blocks for visceral cancer pain management. An evidence-based assessment in published trials was generally poor due to some limitations. According to the review, sympathetic blocks resulted in decreases in pain, opioid consumption, and opioid-induced side effects. CBP is a strong recommendation for patients with pancreatic cancer, while there is a weak recommendation for SHBP.

Commonly occurring among patients with GI and gynecologic cancers, acute and sub-acute intestinal obstructions are important causes of abdominal pain. These obstructions are estimated to occur in 10–28.4% of colorectal cancers [157]. Colicky abdominal pain, distension, nausea, vomiting, and the absence of stools or emission of flatus are common symptoms in malignant bowel obstruction. Symptom palliation for GI symptoms and pain is crucial but does not affect the potential surgical or curative outcome. The most commonly used medical agents to treat symptoms are steroids and anti-secretory and antiemetic agents. Opioids can rarely be omitted, as acute pain also needs to be addressed. The adverse effects of opioids should be taken into consideration, especially for GI dysmotility in patients with malignant bowel obstruction. Consequently, it is important to manage cancer pain based upon its frequency as well as its adverse impact on quality of life for patients and their families.

Skin Problems in Gastrointestinal Cancers

Agents used in cancer treatment may cause a range of skin and nail changes. Chemotherapy affects fast-growing cells such as skin and nail cells. Rash, angioedema, urticaria, and contact dermatitis are more likely in patients who receive chemotherapy. Targeted therapies may cause some specific skin toxicities. In addition, patients who receive radiation therapy have skin reactions, color changes, and recall phenomena.

Skin Problems with Common Cytotoxic Agents

The most important toxicities with cytotoxic agents are alopecia and stomatitis. Usually, hair loss starts within 2–4 weeks after treatment (e.g., anthracycline, which is used in gastric cancer) and regrows within the 3–6 months after completion of the treatment. Stomatitis occurs in about 40% of patients and especially within the first weeks of therapy. Oral care is important before chemotherapy and isotonic mouthwashes are helpful for treating stomatitis [158, 159].

Nail changes seem to occur in regimens containing taxanes and epidermal growth factor receptor (EGFR) inhibitors [160, 161]. Capecitabine (28–74% of patients) and 5-fluorouracil (34% of patients receiving continuous infusion and 13% of patients receiving bolus injection), which are commonly used in GI cancers, may cause a dose-limiting cutaneous toxicity called palmoplantar erythrodysesthesia (PPE). It manifests with palmar and plantar erythema, edema, and dysesthesia with varying degrees of pain, scaling, and vesiculation. It usually occurs within the first 2–12 days after using the drug [162]. A small clinical trial has shown that treatment with vitamin B6 can reduce the symptoms of hand-foot syndrome [163]. However, pyridoxine has been found to not be effective for PPE associated with capecitabine in a randomized, double-blind, placebo-controlled study [164]. Patients taking celecoxib with capecitabine had a low incidence of PPE in retrospective studies [162]. Systemic and topical corticostreoids have been studied; positive and negative results have been found [165, 166]. The important issue is preventing this syndrome by avoiding high temperatures, heavy exercises, tight clothes and shoes, and using emollients and keratolytics [162].

Skin Problems with Targeted Therapies

In recent years, targeted therapies are commonly used in GI cancers. Multi-tyrosine kinase inhibitors (as sunitinib, sorafenib)—used in GI neuroendocrine tumors, GI stromal tumors, and hepatocellular carcinoma—may also cause PPE, with 10–28% of patients treated with sunitinib and 10–62% of patients treated with sorafenib. Treatment is similar to PPE associated with capecitabine [162].

The epidermal growth factor receptor is often overexpressed or dysregulated in GI cancers. The EGFR-mediated signaling pathway-targeting agents (cetuximab and panitumumab) are increasingly part of the treatment of colorectal carcinoma. The toxicity profile of these drugs is commonly characterized by a papulopustular reaction involving the skin. EGFR inhibition may cause follicular occlusion and altered microflora; this results an immune response and inflammation [167]. Patients experience sensorial disease with erythema and edema within the first week of treatment. The papulopustular eruption occurs from weeks 1 to 3, followed by crusting at week 4. Erythema and dry skin may persist through 4 to 6 weeks despite the successful treatment [168].

The management of skin toxicity induced by anti-EGFR therapies is mostly empiric and supportive. Few management guidelines for EGFR-inhibitor-mediated dermatologic toxic effects are published, but most of them are not evidence-based [169]. Prophylactic use of oral tetracycline may be effective, topical tazarotene is ineffective, and topical pimecrolimus is ineffective in randomized controlled trials [170–172]. In general, recommendations are use of gentle shampoos and soaps, moisturizing skin, use of high sun-protective factor creams, and avoiding topical acne medications such as retinoids.

Treatment for skin reactions induced by anti-EGFR therapies varies by grades. The National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 or 4.0 can be used. But according to some opinions, the Pérez-Soler grading system better reflects the specific skin toxicities than the NCI-CTCAE [173]. In grade 1 (mild) acneiform rashes, recommended treatment is topical clindamycin 2% with hydrocortisone 1% (if rash continues after 2 weeks). Systemic treatment should be started if skin reactions are grade ≥ 2 and oral minocycline or doxycycline should be added to topical therapies. In grade 3 (severe) lesions, the treatment should be interrupted until toxicity improves to grade ≤ 2 and the treatment is the same as grade 2. Topical clindamycin 2% with triamcinolone acetonide 0.1% is recommended for scalp lesions in grades 2 and 3. If lesions decrease, dose reduction should be recommended. However, if there is no improvement of severe lesions, the recommendation is to discontinue the anti-EGFR therapies permanently [174].

Skin Problems with Radiation Therapies

Radiation therapy can cause skin to become dry and peel. It can also cause pruritus and skin color changes—turning red or darker. Symptomatic treatment is recommended for cutaneous injury associated with radiation. Recall phenomena is important for medical oncology; it is an acute inflammatory reaction that develops in the previously irradiated areas after receiving chemotherapy. Chemotherapy triggers the skin reaction, and skin becomes red, blisters, peels, or hurts. Radiation recall can occur months or even many years after irradiation, but at least more than 7 days after radiotherapy. In the literature, radiation recall is mostly experienced with capecitabine, which is used in GI cancers. There are no any specific treatment modalities, so symptomatic treatment is recommended for these phenomena [175].

References

1. Cancer Facts & Figures 2018. Atlanta: American Cancer Society. 2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed 12 June 2018.
2. Hui D, Shamieh O, Paiva CE, Perex-Cruz PE, Kwon JH, Muckaden MA, et al. Minimal clinically important differences in the Edmonton Symptom Assessment Scale in cancer patients: a prospective, multicenter study. Cancer. 2015;121(17):3027–35.
3. Kirkova J, Walsh D, Aktas A, Davis MP. Cancer symptom clusters: old concept but new data. Am J Hosp Palliat Care. 2010;27(4):282–8.
4. Aktas A. Cancer symptom clusters: current concepts and controversies. Curr Opin Support Palliat Care. 2013;7(1):38–44.
5. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363(8):733–42.
6. Garla P, Waitzberg DL, Tesser A. Nutritional therapy in gastrointestinal cancers. Gastroenterol Clin N Am. 2018;47(1):231–42.
7. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11–48.
8. Strasser F, Bruera ED. Up to date on anorexia and cachexia. Hematol Oncol Clin North Am. 2002;16(3):589–617.
9. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489–95.
10. Strasser F, Bruera E. Cancer anorexia/cachexia syndrome: epidemiology, pathogenesis, and assessment. In: Ripamonti C, Bruera E, editors. Gastrointestinal symptoms in advanced cancer patients. New York: Oxford University Press; 2002.
11. Aoyagi T, Terracina KP, Raza A, Matsubara H, Takabe K. Cancer cachexia, mechanism and treatment. World J Gastrointest Oncol. 2015;7(4):17–29.
12. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491–7.
13. Warren S. The immediate cause of death in cancer. Am J Med Sci. 1932;184:610–3.
14. Davis MP, Dreicer R, Walsh D, Lagman R, LeGrand S. Appetite and cancer associated anorexia: a review. J Clin Oncol. 2004;22(8):1510–7.
15. Yavuzsen T, Walsh D, Davis MP, Kirkova J, Jin T, LeGrand S, et al. Components of the anorexia-cachexia syndrome: gastrointestinal symptom correlates of anorexia. Support Care Cancer. 2009;17(12):1531–41.
16. Kirkova J, Davis MP, Walsh D, Tiernen E, O'leary N, LeGrand SB, et al. Cancer symptom assessment instruments: a systematic review. J Clin Oncol. 2006;24(9):1459–73.
17. Davis MP, Yavuzsen T, Kirkova J, Walsh D, Karafa M, LeGrand S, et al. Validation of a simplified anorexia questionnaire. J Pain Symptom Manag. 2009;38(5):691–7.
18. Andreyev HJ, Norman AR, Oates J, Cunnigham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer. 1998;34(4):503–9.
19. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Ann Oncol. 2014;25(8):1492–9.
20. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to QOL, exercise capacity and survival in unselected palliative care patients. Support Care Cancer. 2013;21(6):1569–77.
21. Trajkovic-Vidakovic M, de Graeff A, Voest EE, Teunissen SC. Symptoms tell it all: a systematic review of the value of symptom assessment to predict survival in advanced cancer patients. Crit Rev Oncol Hematol. 2012;84(1):130–48.
22. Mei KL, Batsis JA, Mills JB, Holubar SD. Sarcopenia and sarcopenic obesity: do they predict inferior oncologic outcomes after gastrointestinal cancer surgery? Perioper Med (Lond). 2016;5:30.
23. Anandavadivelan P, Brismar TB, Nilsson M, Johar AM, Martin L. Sarcopenic obesity: a probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. Clin Nutr. 2016;35(3):724–30.
24. Chow R, Bruera E, Chiu L, Chow S, Chiu N, Lam H, et al. Enteral and parenteral nutrition in cancer patients: a systematic review and meta-analysis. Ann Palliat Med. 2016;5(1):30–41.
25. Stephenson J, Davies A. An assessment of etiology-based guidelines for the management of nausea and vomiting in patients with advanced cancer. Support Care Cancer. 2006;14:348–53.
26. Wickham R. Evolving treatment paradigms for chemotherapy-induced nausea and vomiting. Cancer Control. 2012;19(2 Suppl):3–9.
27. Darmani NA, Crim JL, Janoyan JJ, Abad J, Ramirez J. A re-evaluation of the neurotransmitter basis of chemotherapy-induced immediate and delayed vomiting: evidence from the least shrew. Brain Res. 2009;1248:40–58.
28. Gordon P, Le Grand SB, Walsh D. Nausea and vomiting in advanced cancer. Eur J Pharmacol. 2014;722:187–91.
29. Oosten AW, Oldenmenger WH, Mathijssen RH, van der Rijt CC. A systematic review of prospective studies reporting adverse events of commonly used opioids for cancer related pain: a call for the use of standardized outcome measures. J Pain. 2015;16(10):935–46.
30. Donthireddy KR, Ailawadhi S, Nasser E, Schiff MD, Nwogu CE, Nava HR, et al. Malignant gastroparesis: pathogenesis and management of an under recognized disorder. J Support Oncol. 2007;5(8):355–63.
31. Davis MP, Walsh D, Lagman R, Yavuzsen T. Early satiety in cancer patients: a common and important but under recognized symptom. Support Care Cancer. 2006;14(7):693–8.
32. Warr DG. Chemotherapy and cancer related nausea and vomiting. Curr Oncol. 2008;15(Suppl 1):4–9.
33. Aprile G, Rihawi K, De Carlo E, Sonis ST. Treatment-related gastrointestinal toxicities and advanced colorectal or pancreatic cancer: a critical update. World J Gastroenterol. 2015;21(41):11793–803.
34. Poon M, Hwang J, Dennis K, DeAngelis C, Zhang L, Chung H, et al. A novel prospective descriptive analysis of nausea and vomiting among patients receiving gastrointestinal radiation therapy. Support Care Cancer. 2016;24(4):1545–61.
35. Bouganim N, Dranitsaris G, Hopkins S, Vandermeer L, Godbout L, Dent S, et al. Prospective validation of risk prediction indexes for acute and delayed chemotherapy-induced nausea and vomiting. Curr Oncol. 2012;19(6):e414–21.
36. Sullivan JR, Leyden MJ, Bell R. Decreased cisplatin-induced nausea and vomiting with chronic alcohol ingestion. N Engl J Med. 1983;309(13):796.
37. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials: a review. Ann Oncol. 1991;2(2):107–14.
38. Roila F, Tonato M, Basurto C, Bella M, Passalacqua R, Morsia D, et al. Antiemetic activity of high doses of metoclopramide combined with methylprednisolone versus metoclopramide alone in cisplatin-treated cancer patients: a randomized double-blind trial of the Italian Oncology Group for Clinical Research. J Clin Oncol. 1987;5(1):141–9.

39. Kris MG, Urba SG, Schwartzberg LS. Clinical round table monograph. Treatment of chemotherapy-induced nausea and vomiting: a post-MASCC 2010 discussion. Clin Adv Hematol Oncol. 2011;9(1):supp1–15.
40. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008;358(23):2482–94.
41. Grunberg SM, Osoba D, Hesketh PJ, Gralla RJ, Borjeson S, Rapoport BL, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity–an update. Support Care Cancer. 2005;13(2):80–4.
42. Schwartzberg L. Chemotherapy-induced nausea and vomiting: state of the art in 2006. J Support Oncol. 2006;4(2 Suppl 1):3–8.
43. Hesketh PJ, Sanz-Altamira P, Bushey J, Hesketh AM. Prospective evaluation of the incidence of delayed nausea and vomiting in patients with colorectal cancer receiving oxaliplatin-based chemotherapy. Support Care Cancer. 2012;20(5):1043–7.
44. Schwartzberg L. Addressing the value of novel therapies in chemotherapy-induced nausea and vomiting. Expert Rev Pharmacoecon Outcomes Res. 2014;14(6):825–34.
45. Sekine I, Segawa Y, Kubota K, Saeki T. Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. Cancer Sci. 2013;104(6):711–7.
46. Roscoe JA, Morrow GR, Hickok JT, Stern RM. Nausea and vomiting remain a significant clinical problem: trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in community clinical practices. J Pain Symptom Manag. 2000;20(2):113–21.
47. Hesketh PJ, Bohlke K, Kris MG. Antiemetics: American Society of Clinical Oncology clinical practice guideline update summary. J Oncol Pract. 2017;13(12):825–30.
48. Morrow GR, Roscoe JA, Kirshner JJ, Hynes HE, Rosenbluth RJ. Anticipatory nausea and vomiting in the era of 5-HT3 antiemetics. Support Care Cancer. 1998;6(3):244–7.
49. Morrow GR, Roscoe JA, Hickok JT. Nausea and vomiting. In: Holland JC, Breitbart W, Jacobsen PB, et al., editors. Psycho-oncology. New York: Oxford University Press; 1998. p. 476–84.
50. Malik IA, Khan WA, Qazilbash M, Ata E, Butt A, Khan MA. Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute, and delayed nausea and vomiting induced by high doses of cisplatin. A prospective randomized trial. Am J Clin Oncol. 1995;18(2):170–5.
51. Aapro MS, Molassiotis A, Olver I. Anticipatory nausea and vomiting. Support Care Cancer. 1995;13(2):117–21.
52. Ravazi D, Delvaux N, Farvacques CJ, De Brier F, Van Heer C, Kaufman L, et al. Prevention of adjustment disorders and anticipatory nausea secondary to adjuvant chemotherapy: a double- blind, placebo-controlled study assessing the usefulness of a alprazolam. J Clin Oncol. 1993;11(7):1384–90.
53. Carey MP, Burish TG. Etiology and treatment of the psychological side effects associated with cancer chemotherapy: a critical review and discussion. Psychol Bull. 1988;104(3):307–25.
54. Lyles JN, Burish TG, Krozely MG, Oldham RK. Efficacy of relaxation training and guided imagery in reducing the aversiveness of cancer chemotherapy. J Consult Clin Psychol. 1982;50(4):509–24.
55. Redd WH, Andresen GV, Minagawa RY. Hypnotic control of anticipatory emesis in patients receiving cancer chemotherapy. J Consult Clin Psychol. 1982;50(1):14–9.
56. Morrow GR, Morrell C. Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. N Engl J Med. 1982;307(24):1476–80.
57. Hesketh PJ, Bohlke K, Lyman GH, Basch E, Chesney M, Clark-Snow RA, et al. Antiemetics: American Society of Clinical Oncology focused guideline update. J Clin Oncol. 2016;34(4):381–6.
58. Tageja N, Groninger H. Chemotherapy-induced nausea and vomiting: an overview and comparison of three consensus guidelines. Postgrad Med J. 2016;92(1083):33–40.
59. Lotfi-Jam K, Carey M, Jefford M, Schofield P, Charleson C, Aranda S. Nonpharmacologic strategies for managing common chemotherapy adverse effects: a systematic review. J Clin Oncol. 2008;26(34):5618–29.
60. Miroddi M, Sterrantino C, Simonelli I, Ciminata G, Philips RS, Calapai G. Risk of grade 3-4 diarrhea and mucositis in colorectal cancer patients receiving anti-EGFR monoclonal antibodies regimens: a meta-analysis of 18 randomized controlled clinical trials. Crit Rev Oncol Hematol. 2015;96(2):355–61.
61. Lee CS, Ryan EJ, Doherty GA. Gastro-intestinal toxicity of chemotherapeutics in colorectal cancer: the role of inflammation. World J Gastroenterol. 2014;20(14):3751–61.
62. Jones JA, Avritscher EB, Cooksley CD, Michelet M, Bekele BN, Elting LS. Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer. Support Care Cancer. 2006;14(6):505–15.
63. Logan RM, Gibson RJ, Bowen JM, Stringer AM, Sonis ST, Keefe DM. Characterization of mucosal changes in the alimentary tract following administration of irinotecan: implications for the pathobiology of mucositis. Cancer Chemother Pharmacol. 2008;62(1):33–41.
64. Sonic ST, Elting RS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004;100(9 Suppl):1995–2025.
65. Andre T, Colin P, Louvet C, Gamelin E, Bouche O, Achille E, et al. Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: results of a randomized trial. J Clin Oncol. 2003;21(15):2896–903.
66. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352(26):2696–704.
67. Yuan A, Kurtz SL, Barysauskas CM, Pilotte AP, Wagner AJ, Treister NS. Oral adverse events in cancer patients treated with VEGFR-directed multitargeted tyrosine kinase inhibitors. Oral Oncol. 2015;51(11):1026–33.
68. Grothey A, Georga S, van Cutsem E, Blsy JY, Sobrero A, Demetri GD. Optimizing treatment outcomes with regorafenib: personalized dosing and other strategies to support patient care. Oncologist. 2014;19(6):669–80.
69. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, et al., The Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;120(10):1453–61.
70. Feldman JM. Carcinoid tumors and syndrome. Semin Oncol. 1987;14(3):237–46.
71. Narayanan S, Kunz PL. Role of somatostatin analogues in the treatment of neuroendocrine tumors. Hematol Oncol Clin North Am. 2016;30(1):163–77.
72. Dillon JS, Chandrasekharan C. Telotristat ethyl: a novel agent for the therapy of carcinoid syndrome diarrhea. Future Oncol. 2018;14(12):1155–64.
73. Pusceddu S, De Braud F, Festinese F, Bregant C, Lorenzoni A, Maccauro M, et al. Evolution in the treatment of gastroenteropancreatic-neuroendocrine neoplasm, focus on systemic therapeutic options: a systematic review. Future Oncol. 2015;11(13):1947–59.
74. van Rossum PSN, Mohammad NH, Vleggaar FP, van Hillegersberg R. Treatment for unresectable or metastatic oesophageal cancer: current evidence and trends. Nat Rev Gastroenterol Hepatol. 2018;15(4):235–49.
75. Doosti-Irani A, Mansournia MA, Rahimi-Foroushani A, Haddad P, Holakouie-Naieni K. Complications of stent placement in

patients with esophageal cancer: a systematic and network analysis. PLoS One. 2017;12(10):e0184784.
76. Miller G, Boman J, Shrier I, Gordon PH. Small-bowel obstruction secondary to malignant disease: an 11-year audit. Can J Surg. 2000;43(5):353–8.
77. Baines M, Oliver DJ, Carter RL. Medical management of intestinal obstruction in patients with advanced malignant disease. A clinical and pathological study. Lancet. 1985;2(8462):990–3.
78. Librach SL, Horvath AN, Langlois EA. Malignant bowel obstruction. In: Palliative Medicine – a case based manual. 2nd ed. New York: Oxford University Press Inc.; 2005. p. 213–7.
79. Anthony T, Baron T, Mercadante S, Green S, Chi D, Cunningham J, et al. Report of the clinical protocol committee: development of randomized trials for malignant bowel obstruction. J Pain Symptom Manag. 2007;34(Suppl 1):49–59.
80. Tuca A, Guell E, Martinez-Losada E, Codorniu N. Malignant bowel obstruction in advanced cancer patients: epidemiology, management, and factors influencing spontaneous resolution. Cancer Manag Res. 2012;4:159–69.
81. Tuca A, Codorniu N, Garzón, Serrano G. Malignant bowel obstruction due to advanced cancer in palliative care: observational and descriptive study. 5th Research Forum of European Association for Palliative Care; May 2008; Trodheim, Norway. Poster: 462.
82. Laval G, Marcelin-Benazech B, Guirimand F. Recommendations for bowel obstruction with peritoneal carcinomatosis. J Pain Symptom Manag. 2014;48(1):75–91.
83. Francescutti V, Miller A, Satchidanand Y. Management of bowel obstruction in patients with stage IV cancer: predictors of outcome after surgery. Ann Surg Oncol. 2013;20(3):707–14.
84. Ripamonti C, Twycross R, Baines M, Bozzetti F, Capri S, De Conno F, et al. Clinical-practice recommendations for the management of bowel obstruction in patients with end-stage cancer. Support Care Cancer. 2001;9(4):223–33.
85. Smith EM, Jayson GC. The current and future management of malignant ascites. Clin Oncol (R Coll Radiol). 2003;15(2):59–72. (review).
86. Nagy JA, Herzberg KT, Dvorak JM, Dvorak HM. Pathogenesis ascites formation: initiating events that lead to fluid accumulation. Cancer Res. 1993;53:2631–43.
87. Lee CW, Bociek G, Faught W. A survey of practice in management of malignant ascites. J Pain Symptom Manag. 1998;16(2):96–101.
88. Fleming ND, Alvarez-Secord A, Von Grueningen V, Miller MJ, Abernetjy AP. Indwelling catheters for the management of refractory malignant ascites: a systematic literature overview and retrospective chart review. J Pain Symptom Manag. 2009;38(3):341–9.
89. Randle RW, Sweet KR, Swords DS, Shen P, Stewart JH, Levine EA, et al. Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites. Ann Surg Oncol. 2014;21(5):1474–9.
90. Cavazzoni E, Bugiantella W, Graziosi L, Franceschini MS, Donini A. Malignant ascites: pathophysiology and treatment. Int J Clin Oncol. 2013;18(1):1–9.
91. Boulay BR, Parepally M. Managing malignant biliary obstruction in pancreas cancer: choosing the appropriate strategy. World J Gastroenterol. 2014;20(28):9345–53.
92. Ho CS, Warkentin AE. Evidence based decompression in malignant biliary obstruction. Korean J Radiol. 2012;13(S1):S56–61.
93. Franc M, Michalski B, Kuczerawy I, Szuta J, Skrzypulec-Plinta V. Cancer related fatigue syndrome in neoplastic diseases. Prz Menopauzalny. 2014;13(6):352–5.
94. Huang X, Zhang Q, Kang X, Song Y, Zhao W. Factors associated with cancer-related fatigue in breast cancer patients undergoing endocrine therapy in an urban setting: a cross-sectional study. BMC Cancer. 2010;10:453.
95. Pettersson G, Berterö C, Unosson M, Börjeson S. Symptom prevalence, frequency, severity, and distress during chemotherapy for patients with colorectal cancer. Support Care Cancer. 2014;22(5):1171–9.
96. Li SX, Liu BB, Lu JH. Longitudinal study of cancer-related fatigue in patients with colorectal cancer. Asian Pac J Cancer Prev. 2014;15(7):3029–33.
97. Arndt V, Merx H, Stegmaier C, Ziegler H, Brenner H. Restrictions in QOL in colorectal cancer patients over three years after diagnosis: a population based study. Eur J Cancer. 2006;42(12):1848–57.
98. O'Gorman C, Denieffe S, Gooney M. Literature review: preoperative radiotherapy and rectal cancer impact on acute symptom presentation and QOL. J Clin Nurs. 2013;23(3–4):333–51.
99. Stauder MC, Romero BK, Atherton DG, Deschamps C, Jatoi A, Sloan JA, et al. Overall survival and self-reported fatigue in patients with esophageal cancer. Support Care Cancer. 2013;21(2):511–9.
100. Kitano T, Tada H, Nishimura T, Teramukai S, Kanai M, Nishimura T, et al. Prevalence and incidence of anemia in Japanese cancer patients receiving outpatient chemotherapy. Int J Hematol. 2007;86(1):37–41.
101. Vardy J, Dhillon HM, Pond GR, Rourke SB, Xu W, Dodd A, et al. Cognitive function and fatigue after diagnosis of colorectal cancer. Ann Oncol. 2014;25(12):2404–12.
102. Scott JA, Lasch KE, Barsevick AM, Piault-Louis E. Patient's experiences with cancer-related fatigue: a review and synthesis of qualitative research. Oncol Nurs Forum. 2011;38(3):E191–203.
103. Lin J-M, Brimmer DJ, Maloney EM, Nyarko E, Belue R, Reeves WC. Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. Popul Health Metrics. 2009;7:18.
104. Brola W, Ziomek M, Czernicki J. Fatigue syndrome chronic neurological disorder. Neurol Neurochir Pol. 2007;41(4):340–9.
105. Minton O, Stone PC. The use of proteomics as a research methodology for studying cancer-related fatigue: a review. Palliat Med. 2010;24(3):310–6.
106. Popiela T, Lucchi R, Giongo F. Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. Eur J Cancer Clin Oncol. 1989;25(12):1823–9.
107. De Conno F, Martini C, Zecca E, Balzarini A, Venturino P, Groff L, et al. Megestrol acetate for anorexia in patients with far-advanced cancer: a double-blind controlled clinical trial. Eur J Cancer. 1998;34(11):1705–9.
108. Lower EE, Fleishman S, Cooper A, Zeldis J, Faleck H, Yu Z, et al. Efficacy of dexmethylphenidate for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. J Pain Symptom Manag. 2009;38(5):650–62.
109. Bruera E, Yennurajalingam S, Palmer JL, Perez-Cruz PE, Frisbee-Hume S, Allo J, et al. Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. J Clin Oncol. 2013;31(19):2421–7.
110. Spathis A, Dhillan R, Booden D, Forbes K, Vrotsou K, Fife K. Modafinil for the treatment of fatigue in lung cancer: a pilot study. Palliat Med. 2009;23:325–31.
111. Barton DL, Liu H, Dakhil SR, Linquist B, Sloan JA, Nichols CR, et al. Wisconsin ginseng (*Panax quinquefolius*) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. J Natl Cancer Inst. 2013;105(16):1230–8.
112. Jensen W, Baumann FT, Stein A, Bloch W, Bokemeyer C, de Wit M, et al. Exercise training in patients with advanced gastrointestinal cancer undergoing palliative chemotherapy: a pilot study. Support Care Cancer. 2014;22(7):1797–806.
113. Pachman DR, Price KA, Carey EC. Nonpharmacologic approach to fatigue in patients with cancer. Cancer. 2014;20(5):313–8.

114. Maguire D, O'Sullivan GC, Collins JK, Morgan J, Shanahan F. Bone marrow micro-metastases and gastrointestinal cancer detection and significance. Am J Gastroenterol. 2000;95:1644–51.
115. Wang Y, Probin V, Zhou D. Cancer therapy-induced residual bone marrow injury-mechanisms of induction and implication for therapy. Curr Cancer Ther Rev. 2006;2(3):271–9.
116. Varma A, Spier BJ, Pfau PR, Safdar N. A case of newly diagnosed metastatic pancreatic cancer presenting with associated immune thrombocytopenic purpura. Wis Med J. 2009;108(9):459–61.
117. Zhu A, Kaneshiro M, Kaunitz JD. Evaluation and treatment of iron deficiency anemia: a gastroenterological perspective. Dig Dis Sci. 2010;55(3):548–59.
118. Yachimski PS, Friedman LS. Gastrointestinal bleeding in the elderly. Nat Clin Pract Gastroenterol Hepatol. 2008;5(2):80–93.
119. Pelesof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010;85(9):838–54.
120. Reese JA, Bougie DW, Curtis BR, Terrell DR, Vesely SK, Aster RH, et al. Drug-induced thrombotic microangiopathy: experience of the Oklahoma Registry and the Blood Center of Wisconsin. Am J Hematol. 2015;90(5):406–10.
121. Niu J, Mims MP. Oxaliplatin-induced thrombotic thrombocytopenic purpura: case report and literature review. J Clin Oncol. 2012;30(31):1705.
122. Mimica M, Tomic M, Babic E, Karin M, Bevanda M, Alfirevic D, et al. Gastric cancer with bone marrow invasion presenting as severe thrombocytopenia. Turk J Gastroenterol. 2014;25(Suppl 1):229–30.
123. Arslan D, Uysal M, Tatli AM, Gunduz S, Sezgin-Goksu S, Bassorgun CI, Coskun HS, Bozcuk H, Savas B. Her-2 positive gastric cancer presented with thrombocytopenia and skin involvement: a case report. Case Rep Oncol Med. 2014;2014:194636.
124. Yazdi MF, Hashemian Z, Nazmieh H, Ghadimi H. A report of three cases with thrombotic thrombocytopenic purpura (TTP) secondary to an occult gastric adenocarcinoma. Pak J Med Sci. 2009;25(4):689–92.
125. Lechner K, Obermeier HL. Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. Medicine. 2012;91(4):1–11.
126. Khorana AA. Cancer-associated thrombosis: updates and controversies. Hematology Am Soc Hematol Educ Program. 2012;2012:626–30.
127. Khorana AA, Fine RL. Pancreatic cancer and thromboembolic disease. Lancet Oncol. 2004;5(11):655–63.
128. Sheth RA, Niekamp A, Quencer KB, Shamoun F, Knuttinen MG, Naidu S, et al. Thrombosis in cancer patients: etiology, incidence, and management. Cardiovasc Diagn Ther. 2017;7(Suppl):S178–85.
129. Chai-Adisaksopha C, Iorio A, Crowther MA, de Miguel J, Salgado E, Zdraveska M, et al. Vitamin K antagonists after 6 months of low-molecular-weight heparin in cancer patients with venous thromboembolism. Am J Med. 2017;131(4):430–7. pii: S0002-9343(17)31277-9.
130. Elalamy I, Mahe I, Ageno W, Meyer G. Long term treatment of cancer associated thrombosis: the choice of the optimal anticoagulant. J Thromb Haemost. 2017;15(5):848–57.
131. Melosky B. Supportive care treatments for toxicities of anti-egfr and other targeted agents. Curr Oncol. 2012;19(Suppl 1):S59–63.
132. De Loughery TG, Beer TM. Bevacizumab and thrombosis: some answers but questions remain. Cancer. 2015;121(7):975–7.
133. Newton HB. Neurological complications of systemic cancer. Am Fam Physician. 1999;59(4):878–86.
134. Giglio P, Gilbert MR. Neurological complications of cancer and treatment. Curr Oncol Rep. 2010;12(1):50–9.
135. Sio TT, Paredes M, Uzair C. Neurological manifestation of colonic adenocarcinoma. Rare Tumors. 2012;4(2):e32.
136. Bano N, Najam R, Mateen A. Neurological adverse effects in patients of advanced colorectal carcinoma treated with different schedules of FOLFOX. Chemother Res Pract. 2013;2013:379870.
137. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32(18):1941–67.
138. Klicovac T, Djurdjevic A. Psychological aspects of the cancer patients' education: thoughts, feelings, behavior and body reaction of patients faced with diagnosis of cancer. J BUON. 2010;15(1):153–6.
139. Deckx L, van Abbema DL, van den Akker M, van den Broeke C, van Driel M, Bulens P, et al. A cohort study on the evolution of psychosocial problems in older patients with breast or colorectal cancer: comparison with younger cancer patients and older primary care patients without cancer. BMC Geriatr. 2015;15:79.
140. Vardy JL, Dhillon HM, Pond GR, Rourke SB, Bekele T, Renton C, et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. J Clin Oncol. 2015;33(34):4085–92.
141. Detrich J, Prust M, Kaiser J. Chemotherapy, cognitive impairment and hippocampal toxicity. Neuroscience. 2015;309:224–32.
142. Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. Palliat Med. 2004;18(3):184–94.
143. Merskey H, Bugduk N. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. 2nd ed. Seattle: IASP Press; 1994.
144. Van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, Van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007;18(9):1437–49.
145. Homsi J, Walsh D, Rivera N, Rybicki LA, Nelson KA, LeGrand SB, et al. Symptom evaluation in palliative medicine: patient report vs systematic assessment. Support Care Cancer. 2006;14(5):444–53.
146. Breivik H, Cherny N, Collett B, de Conno F, Filbet M, Foubert AJ, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Ann Oncol. 2009;20(8):1420–33.
147. Pathophysiology of cancer pain and opioid tolerance. In: The British Pain Society's cancer pain management. 2010. https://www.britishpainsociety.org/static/uploads/resources/files/book_cancer_pain.pdf. Accessed 12 June 2018.
148. Grond S, Zech D, Difenbach C, Radburgh L, Lehmann KA. Assessment of the cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. Pain. 1996;64(1):107–14.
149. Walsh D. Pharmacological management of cancer pain. Semin Oncol. 2000;27(1):45–63.
150. Vielhaber A, Portenoy RK. Advances in cancer pain management. Hematol Oncol Clin North Am. 2002;16(3):527–41.
151. Stacey B. Management of peripheral neuropathic pain. Am J Phys Med Rehabil. 2005;84(3):S4–S16.
152. Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain. 2012;153(2):359–65.
153. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with and without, oxaliplatin as first-line treatment in advanced cancer. J Clin Oncol. 2000;18(6):2938–47.
154. Andre T, Boni C, Mounedji-Boudiat L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350(23):2343–51.
155. Briani C, Argyriou A, Izquierd C, Velasco R, Campagnolo M, Alberti P, et al. Long-term course of oxaliplatin-induced polyneuropathy: a prospective 2-year follow-up study. J Peripher Nerv Syst. 2014;19(4):299–306.

156. Mercandante S, Klepstad P, Kurita GP, Sjogren P, Giarratano A, European Palliative Care Research Collaborative Group (EPCRC). Sympathetic blocks for visceral cancer pain management: a systematic review and EAPC recommendations. Crit Rev Oncol Hematol. 2015;96(3):577–83.
157. Ripamonti C, De Conno F, Ventafridda V, Rossi B, Baines MJ. Management of bowel obstruction in advanced and terminal cancer patients. Ann Oncol. 1993;4(1):15–21.
158. Alexandrescu DT, Wiernik PH, Dutcher JP. Chapter 90. Chemotherapy toxicities and complications. In: Young NS, Gerson SL, High KA, editors. Clinical hematology. Philadelphia: Mosby Elsevier; 2006. p. 1144–54.
159. Kurkjian DC, Ozer H. Management of adverse effects of treatment. In: Devita VT, Lawrence TS, Rosenberg SA, Weinberg RA, editors. DeVita, Hellman and Rosenberg's cancer: principles & practice of oncology. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 2617–38.
160. Minisini AM, Tosti A, Sobrero AF, Mansutti M, Piraccini BM, Sacco C, et al. Taxane induced nail changes: incidence, clinical presentation and outcome. Ann Oncol. 2003;14(2):333–7.
161. Robert C, Sibaud V, Mateus C, Verschoore M, Charles C, Lanoy E, et al. Nail toxicities induced by systemic anticancer treatments. Lancet Oncol. 2015;16(4):e181–e9.
162. Lipworth AD, Robert C, Zhu A. Hand-foot syndrome (Hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. Oncology. 2009;77(5):257–71.
163. Fabian CJ, Molina R, Slavik M, Dahlberg S, Giri S, Stephens R. Pyridoxine therapy for palmar-plantar erythrodysesthesia associated with continuous 5-fluorouracil infusion. Investig New Drugs. 1990;8(1):57–63.
164. Kang YK, Lee SS, Yoon DH, Lee SY, Chun YJ, Kim MS, et al. Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: results of a randomized, double blind, placebo-controlled study. J Clin Oncol. 2010;28(24):3824–9.
165. Curran CF, Luce JK. Fluorouracil and palmar-plantar erythrodysesthesia. Ann Intern Med. 1989;111(10):858.
166. Comandone A, Bretti S, La Grotta G, Manzoni S, Bonardi G, Berardo R, et al. Palmar-plantar erythrodysesthesia syndrome associated with 5-fluorouracil treatment. Anticancer Res. 1993; 13(5c):1781–3.
167. Busam KJ, Capodieci P, Motzer R, Kiehn T, Phelan D, Halpern AC. Cutaneous side-effects in cancer patients treated with the ant epidermal growth factor receptor antibody C225. Br J Dermatol. 2001;144(6):1169–76.
168. Lacouture ME, Melosky BL. Cutaneous reactions to anticancer agents targeting the epidermal growth factor receptor: dermatology–oncology perspective. Skin Therapy Lett. 2007;12(6):1–5.
169. Fox LP. Pathology and management of dermatologic toxicities associated with anti-EGFR therapy. Oncology (Williston Park). 2006;20(5 Suppl 2):26–34.
170. Jatoi A, Rowland K, Sloan JA, Gross HM, Fishkin PA, Kahanic SP, et al. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). Cancer. 2008;113(4):847–53.
171. Scope A, Agero AL, Dusza SW, Myskowski PL, Lieb JA, Saltz L, et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. J Clin Oncol. 2007;25(34):5390–6.
172. Scope A, Lieb J, Dusza S, Phelan DL, Myskowski PL, Saltz L, et al. A prospective randomized trial of topical pimecrolimus for cetuximab-associated acne-like eruption. J Am Acad Dermatol. 2009;61(4):614–20.
173. Pérez-Soler R, Delord JP, Halpern A, Kelly K, Krueger J, Sureda BM, et al. HER1/EGFR inhibitor–associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. Oncologist. 2005;10(5):345–56.
174. Melosky B, Burkes R, Rayson D, Alcindor T, Shear N, Lacouture M, et al. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol. 2009;16(1):16–26.
175. Burris HA, Hurtig J. Radiation recall with anticancer agents. Oncologist. 2010;15(11):1227–37.

Index

A
Abdominal compression, 220
Abdominal pain, 567
Ablative proton therapy, 221
Abridged Patient Generated Subjective Global Assessment (aPG-SGA), 380
Acquired immunodeficiency syndrome (AIDS), 330
Actinomycin D, 638
Active Breathing Coordinator™ system, 219–220
Acute colonic obstruction, 565
Acute emesis, 672
Acute nausea and vomiting, 672
Acute ovarian failure (AOF), 634
Adaptive designs, 500
Adaptive immunity, 89, 467
Adenocarcinoma, 1, 2, 411
  clinical staging, 58
  distant metastasis (M), 57
  of duodenum, 455
  histologic grade (G), 57
  with mucinous features, 43
  with neuroendocrine differentiation, 272
  pathological staging, 58
  postneoadjuvant therapy, 58
  primary tumor (T), 57
  regional lymph nodes (N), 57
Adenoma
  with high-grade dysplasia, 40
  low-grade dysplasia, 40
Adenomatous polyposis coli (APC) gene, 5, 620
Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial, 427
Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC), 82
Adjuvant Colon Cancer Endpoints (ACCENT), 496
Adjuvant 5-FU-based therapy, 123–125
Adjuvant radiation therapy, 428, 434, 435
Adjuvant therapy, 470
  rectal cancer, 168 (*see* Rectal cancer)
  resectable metastatic colorectal cancer
    combination therapy, 127
    neoadjuvant treatment, 127
    resected pulmonary metastases, 127, 128
    systemic therapy, 126
  stage I colon cancer, 109
  stage II colon cancer
    5-FU/LEV, 114
    B2 Colon Cancer Trials, 114, 115
    FOLFOX4 vs. LV5FU2, 115
    gene signatures, 116, 117
    microsatellite instability, 115, 116
    NSABP protocols C-01, C-02, C-03, and C-04, 114, 115
    QUASAR phase III trial, 114, 115
  stage III colon cancer
    in elderly patients, 113, 114
    fluoropyrimidine, 110–112
    5-fluorouracil and irinotecan, 112
    microsatellite instability, 115, 116
    oxaliplatin, 111, 112
    with targeted Agents, 113
Adoptive cell transfer therapy (ACT), 468–470
Adrenocortical carcinoma, 211
Adriamycin, 596, 638
Adult Immunization Schedule, 664
Adults with solid cancer, vaccination, 664
  Haemophilus influenzae type b vaccination, 665
  hepatitis A vaccination, 666
  hepatitis B vaccination, 666
  household contacts of immunocompromised patients, 667
  human papillomavirus vaccine, 666
  influenza vaccination, 664
  meningococcal vaccination, 666
  MMR vaccination, 665
  peumococcal vaccination, 664, 665
  poliovirus vaccination, 666, 667
  tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccination, 666
  varicella vaccination, 665
  zoster vaccination, 665
Advanced gastric cancer, palliative gastrectomy, 352
Advanced HCC, radiotherapy
  localized hepatocellular carcinoma and advanced cirrhosis, 221, 222
  palliation of metastases and tumor thrombi, 221
Advanced hepatic cirrhosis, 221
Advanced pancreas carcinoma
  aggressive pain management, 264
  aging, 264
  anorexia, 264
  biomarker
    BRCA1 and 2 gene mutations, 263
    hENT1, 263
    hyaluronan, 263
    SPARC, 263
    UGT1A1 polymorphism, 263
  cachexia, 264
  chemotherapy
    drug toxicity and cost, 256
    Erlotinib, 256
    5-fluorouracil and irinotecan doublet (FOLFIRI) regimen, 258
    FOLFIRINOX (5-FU, leucovorin, oxaliplatin, and irinotecan), 256
    FOLFOX regimen, 257

S. Yalcin, P. Philip (eds.), *Textbook of Gastrointestinal Oncology*, https://doi.org/10.1007/978-3-030-18890-0

Advanced pancreas carcinoma (*cont.*)
gemcitabine and nab-paclitaxel regimen, 256, 257
nanoliposomal encapsulated irinotecan, 257
OFF, 257
second-line therapy, 257
survival and quality of life, 256
first-line therapy with gemcitabine, 260
functional decline, 264
metastases-related symptoms, 264
molecular alteration, 259
nutritional support, 264
ongoing trials, 264
palliative decompressive procedures, 264
post first-line therapy, 257
systemic therapies, challenges, 264
targeted therapeutic approaches
drug resistance mechanism, 258
genetic alternation or pathway, 258
molecular makeup of tumors, 258
treatment, 240
resistance, 264
US Food and Drug Administration, 256
venous thromboembolism, 264
Aflatoxin, 513
Aflibercept, 635, 637
AIDS-related lymphoma, 330
Akt and mammalian target of rapamycin (mTOR), 88
Alcohol, 4
consumption, 5
Alcoholic liver disease, 582
Algenpantucel-L, 262
Alkylating agents, 636
Alliance for Clinical Trials in Oncology (Alliance), 247
Alprazolam, 672
American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) calculator, 396
American Gastroenterological Association (AGA), 388
American Joint Committee on Cancer staging system for HCC, 214
American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system, 316
American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, 383
American Society of Clinical Oncology (ASCO), 240, 280, 363, 375
American Society of Peritoneal Surface Malignancies (ASPSM), 409
AMG337, 87
Amifostine, 674
Ampullary adenocarcinoma
clinical staging, 99
diagnosis, 99
incidence, 99
pancreatobiliary/intestinal subtype, 98
prognostic factors, 99
risk factors, 98
treatment
adjuvant radiation, 100
locally advanced/metastatic disease, 100
Whipple resection, 99, 100
Amsacrine, 638
Amsterdam II criteria, 601
Anal cancer, 436, 437, 521
charged particle therapy, 438
epidemiology, 369
IMRT, 437, 438
Anal intraepithelial neoplasia (AIN), 175, 521
Ancillary methods, 21
Anemia, 677
Angiogenesis inhibition, 482, 483
Angiosarcoma, 47
Angiotrophic lymphoma, 50
Ann Arbor lymphoma staging system, 332, 333, 337
Anorexia-cachexia syndrome (ACS), 670
Anterior parietal peritonectomy, 406
Anthracycline, 680
Antibody-dependent cell-mediated cytotoxicity (Adendritic cellsC), 466
Anticancer therapy, 379
Anticholinergics, 675
Anticipatory nausea and vomiting (ANV), 672
Anti-CTLA-4, 471, 473
Anti-diarrheals, 358
Anti-EGFR therapy, 496
Antiemetics, 671
Anti-epidermal growth factor receptor (EGFR) immunotherapy, 43
Anti-Her2 treatment with trastuzumab, 258
Antimetabolites, 636
Anti-tumor effect, heat, 411
Anti-vascular endothelial growth factor (VEGF) monoclonal antibody, 168
Apatinib, 86
Apendiceal mucinous neoplasms, 101, 102
Apixaban for the Prevention of Venous Thromboembolism in Cancer Patients (AVERT) study, 375
Appendiceal adenocarcinomas
clinical presentation, 101
diagnosis, 101
early stage resectable disease, 103
metastatic disease, 103
peritoneal mucinous carcinomatosis, 101, 102
prognosis, 102
staging, 102
Appendiceal cancer, 100
chemotherapy and debulking procedures, 411
colectomy, 412
cytoreduction, 412
distant/lymphatic metastases, 411
hyperthermic intraperitoneal chemotherapy, 411, 412
intra-abdominal mucin–pseudomyxoma peritonei, 411
laboratory evaluation, 412
malignancy, 411
mitomycin C, 411
mucin production, 411
outcomes, 411
prognosis, 411
pxaliplatin, 411
standard of care, 411
Appendiceal NETs, 271
Appendix with tumor and mucin production, 412
Architectural phenotype, 28
ASCO and the American Academy of Hospice and Palliative Medicine, 363
Asian Esophageal Cancer Belt, 1
Aspirin, 8, 518, 519, 522, 577
Assisted ejaculation techniques, 646
Assisted-reproduction technology (ART), 643
Ataxia, 678
Ataxia-telangiectasia mutated (ATM) gene, 88
Atezolizumab, 473
Atrophy/intestinal metaplasia, 73
Autophagy, 380
Autosomal dominant hereditary pancreatitis, 584
Azathioprine, 663

B
Bacillus Calmette-Guerin (BCG) vaccine, 467
Bannayan-Riley-Ruvalcaba syndrome, 45
Barcelona Clinic Liver Cancer (BCLC) criteria for surgical resection, 217–219, 559
Barrett's esophagus (BE), 522, 533, 538, 540, 541, 575
  screening, 574
Base excision repair (BER), 621
Basket trials, 501, 502
BBI608 molecule, 89
B-cell leukemia/lymphoma 10 (BCL-10), 331
B2 Colon Cancer Trials (IMPACT B2), 114
Belinostat, 625
Benign and malignant neoplasms of liver, 311
Benign small bowel lesions, 270
Benzodiazepines, 671, 672
Berlin-Frankfurt-Munster (BFM-90), 316
Bethesda guidelines, 600, 601
Bevacizumab, 85, 635, 637, 658, 672, 673, 677
  VEGF inhibitors, 150
Biliary decompression, 542
Biliary intervention, 552
Biliary stent placement in neoadjuvant treatment of pancreatic cancer, 543
Biliary stents, types of, 542
Biliary tract cancers (BTCs)
  adjuvant therapy, early stage disease, 185, 186
  advanced/metastatic disease, 187
  BRAFV600E, 191
  critical signaling pathways, 187–188
  downstream signaling pathways
    MAPK pathway, 190
    PI3k/Akt pathway, 190
  EGFR pathway
    cetuximab, 189
    erlotinib, 189
    panitumumab, 189
  epidemiology, 185
  fibroblast growth factor receptors, 191
  gemcitabine/platinum combination therapy, 187
  HER-2 (*HER-2/neu* or *ERBB2*), 190
  IDH1 and *IDH2*, 191
  immunotherapy, 192
  Notch signaling pathway, 192
  OLT, unresectable BTC, 186
  ROS1 fusions, 191, 192
  sites of origin, 185, 186
  VEGF pathway
    bevacizumab, 188
    cerdiranib, 188
    sorafenib, 188
    sunitinib, 188
    vandetanib, 188, 189
Bioelectric impedance analysis, 384
Bioimpedance analysis (BIA), 380
Biologically active dose (BAD), 499
Biologically equivalent dose (BED), 423
Biomarker-driven approaches, 493
Biostatistical model, 249
Bleomycin, 638
Bone marrow suppression, 411
Borborygmi, 674
Borderline resectability, PDAC
  collaborative and objective definition, 237
  definition, 237
  exploratory laparotomy and pancreatectomy, 237
  MDACC definition, 236
  neoadjuvant therapy
    chemoradiation, 245
    definitive surgical therapy, 246
    FOLFIRINOX over gemcitabine, 247
    gemcitabine, 247
    gemcitabine-based chemoradiation, 245
    histologic response to induction, 246
    histopathologic response of tumor cells, 246
    induction chemotherapy, 246
    NCCN clinical practice guidelines, 246
    pathologic response to induction therapy, 246
    patient management, 245
    preoperative therapy, 247
    R0 resection rates, 247
    radiosensitizers, 246
    randomized phase II trial, 245
    resectability and overall survival, 245, 246
    staging, 245
    surgical resection, 246
    survival, 245
    trials, 244
    vascular resection and reconstruction, 247
  nonoperative management, 236
  positive pathologic margins, 236
  tumor-vascular interface, 236
  unresectability, 236
  venous involvement, 236, 237
Borderline resectable tumors, 236
Bowel obstruction, algorithm, 353
Brachytherapy, 433
BRAF, 474
  inhibition, 155
  mutation, 620, 621
BRAFV600E, 191
BRCA gene mutation in patients with pancreas cancer, 263
  BRCA1/2 mutations, 622
BRCAness, 615, 616, 622
Breakthrough nausea and vomiting, 672, 673
Breast cancer, 551, 562
Breast Cancer Linkage Consortium (BCLC), 5
Breathing motion during radiotherapy with image guidance, 220
Brief Fatigue Inventory (BFI), 676
BRIGHTER study, 89
Brivanib, 623
Bronchial asthma, 273
Bronchospasm, 273
Burkitt's lymphoma (BL)/Burkitt's leukemia, 50, 315, 335, 341, 342
Busulfan, 638
Butylbromide, 675

C
CA 19-9, 484
Cabozantinib, 623
Cachexia, 379, 670
Calcification, 452
Calcium, 519
CALGB80101 trial, 82
Cancer and Leukemia Group B (CALGB) Ethics Committee, 495, 498
Cancer-associated thrombosis
  etiology, 372
  hazard ratio, 373
Cancer cachexia
  assessment, 380
  brown adipose tissue, 381

Cancer cachexia (*cont.*)
computerized tomography, 380
dual energy X-ray absorptiometry scan, 380
energy expenditure, 381
hypothalamus, 381
immobility and lethargy, 380
inflammation-induced hypermetabolic (catabolic) state, 380
management, 381, 382
mechanism of, 381
microRNAs, 381
microvesicles, 381
muscle-wasting process, 381
myostatin and activins, 380
nutritional intervention, 380
oxidative stress and mitochondrial dysfunction, 381
pharmacotherapy
anamorelin, 382, 383
cannabinoids, 382
corticosteroids, 382
dronabinol, 382
fish oil/eicosapentaenoic acid, 382
ghrelin, 382, 383
megestrol acetate, 382
selective androgen receptor modulator enobosarm, 382
testosterone replacement, 382
quality of life, 379, 380
ring finger protein, 380
short life expectancy, 379
skeletal muscle atrophy, 381
skeletal muscle protein breakdown, 380
thermogenesis, 381
tolerance to chemotherapy, 380
treatment tolerance, 380
zinc alpha2 glycoprotein, 380
Cancer cells, intracellular signaling pathways, 258
Cancer family syndrome, 597
Cancer Genomic Project (CGP), 613
Cancer genomics
access to tissue, 626
cholangiocarcinoma
FGFR gene fusions, 623, 624
IDH1/2 mutations, 624
immune checkpoint inhibitors, 624
molecular classification, 623
targeted therapies, 624
circulating tumor DNA, 625, 626
colorectal cancer
BRAF mutation, 620, 621
EGFR inhibition, 621
HER2 amplification, 621
MMR status, 621
molecular classification, 620
NTRK gene fusions, 621
Wnt signaling, 620
co-occurring mutations, 625
esophageal/gastric cancer
FGFR2, 619
HER2inhibitors, 618, 619
immune checkpoint inhibitors, 618
molecular classification, 617, 618
PI3K-AKT-mTOR inhibitors, 619
vascular endothelial growth factor receptor blockade, 619
gastroentropancreatic neuroendocrine tumors
molecular analysis, clinical utility of, 625
molecular classifications, 624, 625
genomic complexity, 625
hepatocellular carcinoma, 623
cabozantinib, 623
FGF signaling, 623
molecular classification, 623
pembrolizumab, 623
multiple omics, evaluation of, 625
next-generation sequencing (*see* Next-generation sequencing (NGS))
pancreatic cancer
BRCA1/2 mutations/BRCAness, 622
KRAS mutation, 622
matabolic pathways, 622
mismatch-repair deficiency, 622
molecular classification, 621, 622
nuclear export factors, 622
prioritization, 625
small bowel adenocarcinoma, molecular classification, 619
tumor cell heterogeneity, 626
Cancer grade (cG), 56
Cancer of gallbladder, 185
Cancer-related fatigue (CRF), 676
Cancer-related thrombosis
anti-angiogenic, 370
candidate biomarkers, 372
chemotherapy-related factors, 370–372
genetic determinants, 371
hypercoagulability, 370
platelets-related factors, 370, 371
pro-coagulant factors, 370
prophylaxis, 375
risk assessment tool, 373
thromboembolic events, 369
thrombogenicity, 370
tissue factor, 370
treatment, 376
vasculotoxic, 370
Cancer stem cell, 89
Cancer treatment modulaties
radiation therapy, 659
surgery, 659
systemic therapy, 658, 659
Cancer vaccines, 261, 262
Capecitabine, 434, 619, 635, 637, 638, 658, 672, 678, 680
Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial, 82
Capecitabine-based neoadjuvant chemoradiation, 246
CapeOx-Bev induction therapy, 147
CAPOX (capecitabine and oxaliplatin), 640
Carboplatin, 638, 658, 672
Carcinoembryonic antigen (CEA) assay, 467, 468, 580
Carcinogenesis, 509
Carcinoid crisis, 273, 276
Carcinoids, 455
Carcinoid syndrome
abdominal cramping, 273
bioactive products, 273
cardiac valvular lesions, 273
flushing and diarrhea, 272, 273
multiple secretory polypeptides and amines, 273
muscle wasting, 273
serotonin, 273
severe flushing, 273
somatostatin analogs, 275
symptoms, 273
vasoactive factors, 272

Carcinoid tumors, 272, 674
Carcinoma, 15
Carcinoma in situ (pTis), 52
Carcinomas of unknown primary (CUP), 616
Cardiopulmonary resuscitation, 361
Carmustine, 638
Carney-Stratakis syndrome, 290, 293, 321
Carney triad, 321
Cascade testing, 603
CASSINI study, 375
CD137, *see* 4-1BB
CD223, 472
CD27, 472
CD357, *see* Glucocorticoid-induced TNFR-related protein (GITR)
CD40, 473, 474
  activation, 261
CD40 monoclonal antibody CP-870,893 with full-dose gemcitabine, 261
CD70, 472
CD8 T cells, 467
Celecoxib, 522, 523, 577, 680
Celiac disease, 336
Celiac neurolysis, 567
Celiac plexus block (CPB), 679
  pancreatic cancer, 354
Celiac plexus neurolysis, 354
Cell proliferation and differentiation, 481
Central venous access, 402
Central venous pressure (CVP), 402
Cetuximab, 149, 189, 620, 621, 635, 639, 658, 672, 673, 680
CgA secretion, NETs, 274
Charged particle therapy
  in anal cancer, 438
  in cholangiocarcinoma, 434
  esophageal cancer, 425
  gastric cancer, 428
  in hepatocellular carcinoma, 432, 433
  in pancreatic cancer, 430, 431
  in rectal cancer, 435, 436
Checkpoint inhibitors, 471
Chemoembolization, HCC, 215, 216
Chemoprevention for Barrett's Esophagus Trial (CBET), 522
Chemoradiation (CRT), 424, 428, 437
ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial, 424
Chemotherapy, 658, 659, 663–666, 680
Chemotherapy-free interval (CFI), 145
Chemotherapy-induced nausea and vomiting (CINV), 671
  acute nausea and vomiting, 672
  anticipatory nausea and vomiting, 672
  breakthrough nausea and vomiting, 672, 673
  chronic nausea and vomiting, 672, 673
  delayed nausea and vomiting, 672
  highly emetogenic chemotherapy, 673
  low emetogenic chemotherapy, 673
  minimal emetogenic chemotherapy, 673
  moderately emetogenic chemotherapy, 673
  non-pharmacological strategies, 673
  refractory nausea and vomiting, 672, 673
Chemotherapy-induced peripheral neuropathy (CIPN), 678
Child-Pugh classification, 212
Children
  GIS malignancies
    epithelial origin, 316–318
    lymphoid origin, 315–316
    mesenchymal origin, 321–322
    neuroendocrine origin, 318–321
  hepatic tumors
    blastemal origin, 312–314
    epithelial origin, 314, 315
Chlorambucil, 638
Choi criteria, 300
Cholangiocarcinoma (CCA), 368, 433
  epidemiology, 3
  molecular analysis, clinical utility of
    FGFR gene fusions, 623, 624
    IDH1/2 mutations, 624
    immune checkpoint inhibitors, 624
    targeted therapies, 624
  molecular classification, 623
  particle therapy, 434
  SBRT, 433, 434
  unresectable intrahepatic cholangiocarcinoma, 433
  with VTE screening, 368
Cholangioscopic-guided biopsies, 535
Cholangitis, 552
Chromogranins, NETs, 274
Chromosomal rearrangement of proto-oncogene c-MYC, 343
Chronic atrophic gastritis, 575
Chronic gastroesophageal reflux, 74
Chronic hepatitis B, 581, 582
Chronic hepatitis C, 582
Chronic nausea and vomiting, 672, 673
Chronic pancreatitis, 584
Cigarette smoke, 4
Circulating tumor DNA (ctDNA), 625, 626
Circulation tumor cell (CTCs), 617
Circumferential resection margin (CRM), 52, 117, 118, 162
Cirrhosis, 314, 582
Cisplatin, 558, 619, 635, 637–639, 658, 659, 672, 678
Cisplatin-based therapy, 367, 371
Cisplatin-induced nausea and vomiting, 671
CLARINET trial, 277
Claustrophobia, 449
Clinical trials, 493
  adaptive designs, 494
  benefit and endpoints, maximal preliminary scores, 495
  biomarker-driven approaches, 493
  biomarker identification, ethics of, 498, 499
  data quality, 493
  elderly population, endpoints in, 495
  ESMO-MCBS, 494, 495
  European Medicines Agency's adaptive pathways approach, 494
  maximal preliminary scores, 494
  phase I trials, 499, 500
  phase II trials, 500
    adaptive phase II trials, 500, 501
    innovative biomarker-driven phase II trials, 501, 502
  phase III trials
    adaptive phase III designs, 503
    hazard ratio, 502
  phase IV trials, 504, 505
  precision medicine, 498
  proof of concept, 494
  seamless phase II/III trials, 503
    sample size re-estimation, 503, 504
  surrogate endpoints
    disease-free survival, 496
    objective tumor response and tumor shrinkage, 496–498
    overall survival, 495, 496

Clinical trials (*cont.*)
pathological response, 498
progression-free survival, 496
Coagulopathies in liver disease, 368
Cognitive and behavioral therapy, 676
Cognitive impairment, 676
COIN-B, 148
Coliseum technique, 409
Colitis-associated dysplasia, 42
College of American Pathologists (CAP) checklist, 16, 33, 34
Cologuard®, 580
Colon cancer, 14–15, 458, 459
imaging, 461
CTC, 461
MRC, 461, 462
T staging, 31
Colon Health and Life-Long Exercise Change (CHALLENGE) trial, 514
Colonic obstruction, 545
Colonic polyps, 39
Colonic stenting, 565, 566
Colonoscopy, 578–581
ColoPrint®, 116
Colorectal adenocarcinomas, 42
Colorectal cancer (CRC), 22, 509, 599, 619
adjuvant therapy, 470
adoptive cell therapy, 470
antitumor immune mechanisms
adaptive immunity, 467
immune escape, 465, 466
immune surveillance, 465
immunoediting, 465
innate immunity (*see* Innate immunity)
biomarkers in immunomodulation
BRAF, 474
KRAS, 474
MSI-high, 474
breast, 50
cancer-related deaths, 3
cancer staging, 51
chemotherapy, 369, 414
in children
biopsy, 318
clinical presentation, 317
diagnosis, 317
environmental factors, 317
epidemiology, 317
genetics, 317
histology, 318
incidence, 317
K-ras mutation, 318
laparotomy, 318
localization, 318
staging, 318
survival rates, 318
transanal endoscopic microsurgery, 318
treatment, 318
vague abdominal pain, 317
classification
colonic polyps, 39
colorectal adenocarcinomas, 42
dysplasia, 42
hyperplastic polyps, 40
malignant polyps, 42
sessile serrated adenoma, 40, 41
traditional serrated adenomas, 41
tubular adenomas, 39
clinical staging, 51
clinical utility
BRAF mutation, 620, 621
EGFR inhibition, 621
HER2 amplification, 621
MMR status, 621
NTRK gene fusions, 621
Wnt signaling, 620
colorectal sarcomas
angiosarcoma, 47
fibrosarcoma, 47
Kaposi sarcoma, 47, 48
leiomyosarcomas, 47, 48
lipoleiomyosarcomas, 47
complete cytoreduction, 414, 415
cytokine treatment, 470
diet and prevention
primary, 511, 512
secondary, 512
tertiary, 512, 513
endometrial stromal sarcoma, 50
epidemiology, 368, 369
frequency, 3
GIST, 48, 49
hepatocellular carcinoma, 50
hereditary syndromes
Cronkhite-Canada syndrome, 46
familial adenomatous polyposis, 44
HNPCC/Lynch syndrome, 44
Juvenile polyposis syndrome, 45
MutY-associated polyposis, 44
Peutz-Jegher syndrome, 46
serrated polyps, 44
imaging
CT, 457
MRI, 457
PET-CT, 458
immune checkpoint
4-1BB, 473
CD27, 472
CD40, 473, 474
CD70, 472
cytotoxic T lymphocyte antigen-4 and B7, 471
glucocorticoid-induced TNFR-related protein, 472
lymphocyte activation gene-3, 472
OX40, 473
programmed cell death protein 1, 471
T-cell immunoglobulin and mucin containing protein-3, 472
immunotherapy strategies, 469
adoptive cell transfer therapy, 468, 469
checkpoint inhibitors, 471
cytokines treatment, 469, 471
phase 3 trials, 467, 468
vaccination, 467, 468, 470
incidence, 3, 161, 465
irinotecan with oxalplatin, 414
lymphoma
Burkitt lymphoma, 50
diffuse large B cell lymphoma, 49
extranodal marginal zone lymphoma, 49
follicular lymphoma, 49
Hodgkin's lymphoma, 50
intravascular lymphoma, 50
primary effusion lymphoma, 50
T-cell lymphoma, 50

melphalan, 415
mesothelioma, 50
mitomycin C and oxaliplatin, 414
molecular classification, 620
molecular testing, 43
mortality rates, 3
neuroendocrine tumors, 46, 47
staging, 53
obesity, control of
primary prevention, 515
secondary prevention, 515
tertiary prevention, 515, 516
ovary, 50
palliative surgery, 414
pathological staging, 51–53
pathologic evaluation
large polyps, 37, 38
resection specimen processing, 38, 39
sample processing, 37
small colonic biopsies, 37
TNM staging, 38–39
physical activity
primary prevention, 513, 514
secondary prevention, 514
tertiary prevention, 514
pregnancy, 655
prognosis, 3, 414
prostate and bladder carcinoma, 50
recurrent malignancies/salvage procedures, 415
screening, 580
average risk populations, 577, 581
carcinoembryonic antigen assay, 580
colonoscopy, 578–580
computed tomography colonography, 579
double-contrast barium enema, 579
fecal occult blood testing, 579, 580
flexible sigmoidoscopy, 579
high risk genetic syndromes, 578
high risk populations, 577, 578, 581
incidence of, 577
microRNAs, 580
modalities, 578
risk factors, 577
by sigmoidoscopy, 579
stool-based DNA testing, 580
stomach, 50
survival rate for, 465
therapeutic prevention
aspirin, 518, 519
calcium, 519
chemoprevention studies, 517
HMG-CoA reductase inhibitors (statins), 519
immuno-prevention, 521
metformin, 519
NSAIDs, 518, 519
polyamine inhibitors, 520, 521
vitamin D, 519
tumors of lung, 50
Colorectal Cancer DSA (ColDx)®, 117
Colorectal endoscopic resection, 539
Colorectal lymphomas
adjuvant chemotherapy, 340
baseline laboratory studies, 340
cecum and rectum, 339
chemotherapy-associated bowel perforation, 340
clinical presentation, 340
colonoscopy with biopsy, 340
combined modality approach, 340
double-contrast barium enema, 340
follow-up, 340
gastrointestinal involvement, 339
histopathological evaluation of tissue, 340
HIV, 340
immunosuppression, 340
inflammatory bowel disease, 340
multiple biopsies, 340
non-Hodgkin lymphoma, 339
optimal treatment, 340
PET scan, 340
physical examination, 340
radiation, 340
recurrence, 340
risk factors, 340
surgical resection, 340
Colorectal sarcomas
angiosarcoma, 47
Kaposi sarcoma, 47, 48
leiomyosarcomas, 47, 48
lipoleiomyosarcomas, 47
Colorectal surgery, 369
Combination of Children's Oncology Group (COG) risk groups, 313
Combination therapies for HCC, 217
Combined screening program, 605
Comparative trials with somatostatin analogs, 278
Comparison of Acute Treatments in Cancer Haemostasis (CATCH) study, 376
Complete cytoreduction for appendiceal, colorectal and gastric cancers, 400
Complete cytoreduction versus incomplete cytoreduction, 400
Complete eradication of intestinal metaplasia (CE-IM), 541
Computed tomography (CT)
colorectal cancers, 457
esophageal cancer, 446, 447
gastric adenocarcinoma, 447–449
peritoneal carcinomatosis, 451–453
pregnancy, 657
small bowel, malignant disease of, 454–456
Computed tomography colonography (CTC), 579
colon cancers, 461
Computer-aided detection (CAD) algorithms, 461
Confocal laser endoscopy (CLE), 533
Congenital/acquired immunodeficiency disorders, 336
CONKO-004 trial, 373
Constitutional mismatch repair deficiency (CMMRD), 599
Constricting annular tumors, 22
Continual reassessment method, 499
Controlled ovarian stimulation (COS), 643
Conversion therapy (neoadjuvant), 142, 143
Co-ordinate immune response cluster (CIRC), 474
Corticosteroids, 671, 675, 680
therapy, 663
COUGAR-02 study, 84
Cowden syndrome, 45
CpG island methylation phenotype (CIMP), 620
Crohn's (CD) colitis, 577
Crohn's-like reaction, 598
Crohn-like peritumoral features, 43
Cronkhite-Canada syndrome, 46
Cryoablation, 217, 554
Current Procedural Terminology (CPT) codes, 250
Cyclin dependent kinase inhibitors, 636
Cyclizine, 671

Cyclophosphamide, 638
Cystic pattern, 28
Cytarabine, 638
Cytokine treatment, 469–471
Cytopathologic evaluation, 16–18
Cytopathology specimen submission protocols, 20
Cytoreductive index (CCR), 399
Cytoreductive surgery (CRS), 675
  HIPEC, 409
  peritoneal malignancies
    anterior peritonectomy, 405
    blunt dissection, 406
    bowel integrity, 405
    bowel resections with primary anastomoses, 408
    care, 407
    dissection, 406
    gastrohepatic ligament, 406
    laparoscopic cytoreduction, 404
    laparoscopic evaluation, 404
    large-caliber, self-retaining retractor, 405
    lateral dissection, perinephric tissues and right adrenal gland, 406
    2-layered repair, 408
    lectrocautery, 407
    liver mobilization, 406
    liver reflection, 406
    midline incision, 405
    parietal and visceral peritoneum, 405
    peritonectomies/visceral resections, 405
    peritonectomy intraoperative and completion, 406
    porta hepatis, 406
    rectovaginal septum, 407
    resection of ileocecal valve, 405
    resection of primary tumor, 405
    scissor and knife resections, 405
    subphrenic peritonectomy, 405, 406
    type 1 nodules, 407
    type 2 lesions, 407
    type 3 nodules, 407
    type 4 nodules, 408
    type 5 nodules, 408
    visceral peritoneum, 405
Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC), 395
Cytosar, 638
Cytotoxic antitumor antibiotics, 636
Cytotoxic therapy, 187
Cytotoxic T lymphocyte antigen-4 (CTLA-4), 89, 192, 471
Cytotoxic T lymphocyte-associated molecule-4, 227
Cytoxan, 638

D
Dacarbazine, 638
Daunomycin, 638
Daunorubicin, 638
Dawson's criteria for primary GI lymphoma, 329
Deep venous thrombosis (DVT), 367, 677
Definitive chemoradiotherapy, 61
Delayed nausea and vomiting, 672
Delirium, 678
Depression, GI, 359
Desmoid disease, 596
Desmoplastic stromal reaction, 484
Devascularization of large HCCs, 217
Dexamethasone, 673
Diarrhea, 673
Dietary fiber, 7
Diets, 7
Diffuse gastric cancer, 618
Diffuse large B cell lymphoma (DLBCL), 49, 330, 341
Diffuse tumors, 22
Digestive fistulas, 408
Discontinuous spread, 33
Disease-free survival (DFS), 496
Disseminated primary intra-abdominal disease, 315–316
DNA damage repair, 482
DNA double-strand repair (DDR), 615, 616
DNA mismatch repair (MMR), 43, 621
DNA repair pathways, 260
Docetaxel, 637, 658, 672
Domperidone, 671
Dose-limiting toxicities (DLT), 499
Dose-painted intensity modulated radiation therapy (DP-IMRT), 437
Dose–response evaluation, 7
Double-contrast barium enema (DCBE), 579
Doxorubicin, 558, 560, 596, 638
Doxycycline, 680
Drug-eluting beads (DEBs), 558
Duke Stage A disease, 369
Duloxetine, 678
Duodenal gastrointestinal stromal tumor (GIST), 456
Durvalumab, 473
Dutch population-based case control study, 369
Dysphagia, 67, 673
Dysplasia, 42

E
Early disease
  adenocarcinoma, 59
  adjuvant treatment, 60
  Barrett's esophagus, 59, 60
  endoscopic therapy
    local recurrence rates, 59
    long-term outcomes, 59
    multimodality management, 59
    superficial esophageal cancer, 59
    T1a/T1b tumors, 59, 60
  esophagectomy, 60
  high-grade dysplasia, 59
  lymph node metastases, 59
  metachronous lesions, 59
Early gastric cancer (EGC), 77
Early tumor shrinkage (ETS), 496
Eastern Cooperative Oncology Group (ECOG) Performance Status, 242, 247, 343, 380, 396
EBV-associated B-cell lymphomas, 336
E-cadherin gene (CDH1) mutation, 617, 618
Ectopic crypts, 41
Edmonton Symptom Assessment Scale, 380
Eflornithine, 518, 520, 521
EGFR inhibitors, 149–150, 621
EGFR-MAPK and PI3K pathways, 75
18-gene colon cancer assay, 116
Electron microscopy, 21
Embryo cryopreservation, 642, 643
Embryogenesis, 655
Embryonic pathways, 481, 482
EMR, *see* Endoscopic mucosal dissection (EMR)
Endometrial stromal sarcoma, 50

Endorectal brachytherapy (EBT), 436
in rectal cancer, 436
Endoscopic ablation
endoscopic cryotherapy, 541, 542
radiofrequency ablation, 540, 541
therapies, 522
Endoscopic cryotherapy, 541, 542
Endoscopic full-thickness resection (EFTR), 540
Endoscopic mucosal dissection (EMR), 540
adverse events, 537
technical and clinical outcomes, 536–539
Endoscopic mucosal resection (EMR), 21, 522
Endoscopic resection
endoscopic mucosal resection, 536, 537
adverse events, 537
technical and clinical outcomes, 538, 539
endoscopic submucosal dissection
adverse events, 537, 538
technical and clinical outcomes, 538, 539
techniques, 536, 537
Endoscopic retrograde cholangiopancreatography (ERCP), 534, 585
biliary decompression, 542
biliary stent placement in neoadjuvant treatment of pancreatic cancer, 543
biliary stents, types of, 542
preoperative biliary drainage, 543
Endoscopic spray cryotherapy, 522
Endoscopic submucosal dissection (ESD), 59
adverse events, 537, 538
technical and clinical outcomes, 538, 539
techniques, 536, 537
Endoscopic ultrasonography, esophageal cancer, 446
Endoscopic ultrasound–fine needle aspiration (EUS-FNA), 533, 534
Endoscopic ultrasound–fine needle biopsy (EUS-FNB), 533–535
Endoscopy
GAC, 447
pregnancy, 657
Energy homeostasis, 380
ENETS/WHO Nomenclature and classification for NETs, 271
Engerix-B®, 666
Enteral immunonutrition, 387
Enteral nutrition, 387, 389
Enteral stenting
colonic obstruction, 545
gastric outlet obstruction, 544, 545
malignant esophageal obstruction, 544
small intestinal obstruction, 544, 545
Enteral vs. parenteral nutrition, 386, 388
Enteropathy-associated T-cell disease, 339
Enteropathy-associated T-cell lymphoma (EATL), 335
Entrectinib, 621
EORTC trials, 240
Epidermal growth factor receptor (EGFR)-directed therapies, 136
Epidermal growth factor receptor (EGFR) inhibitors, 86, 87, 167, 200, 480, 637
Epidermal growth factor receptor (EGFR) pathway
cetuximab, 189
erlotinib, 189
panitumumab, 189
Epi proColon®, 580
Epirubicin, 637, 638, 658, 672
Epithelial-mesenchymal transition, 370
Epithelial tumors, 100
Epstein–Barr virus (EBV), 6
in post-transplant lymphoproliferative disorders lymphomagenesis, 330
Erbitux in Combination With Xeloda and Cisplatin in Advanced Esophagogastric Cancer (EXPAND) trial, 86
Erlotinib, 189, 524
Escalation With Overdose Control (EWOC) method, 499
Esophageal adenocarcinoma (EAC), 316, 574
incidence of, 574
risk factors, 574
screening
EGD, 574
recommendations and guidelines, 575
Esophageal cancer (EC), 674
age-standardized incidence rates, 1
AJCC cancer staging categories, 57
AJCC TNM staging, 56
cancer grade, 56
cancer location, 56
in children
chronic irritation, 316
dysphagia and progressive loss of weight, 316
clinical manifestations, 56
CT, 446
definitive CRT, 55
diagnosis, 56, 445
dysphagia, palliative management, 67
early disease
adjuvant treatment, 60
endoscopic therapy, 59, 60
esophagectomy, 60
EGJ staging, 56
epidemiology, 55, 367
esophageal adenocarcinoma, 574
esophageal stenting, 351
etiologic factors, 55, 56
gastrointestinal stenting, 563–565
histological types, 1
imaging
computed tomography, 446, 447
endoscopic US, 446
PET-CT, 447
incidence and mortality rates, 1, 2
locally advanced disease
definitive chemoradiotherapy, 61
neoadjuvant treatment, 61–63
non-operative treatment, 63, 64
unresectable disease, 65, 66
lymphatic dissemination, 445
metastatic disease, 66, 67
molecular analysis, clinical utility of
FGFR2, 619
HER2 inhibitors, 618, 619
immune checkpoint inhibitors, 618
PI3K-AKT-mTOR inhibitors, 619
vascular endothelial growth factor receptor blockade, 619
molecular classification, 617, 618
mortality rate, 1
preoperative CRT, 55
prognostic stage groups, 56–58
radiotherapy, 55
resectable esophagogastric junction adenocarcinomas, 65
risk factors, 1, 574
RT
CALGB 9781 trial, 424
charged particle therapy, 425

Esophageal cancer (EC) (*cont.*)
chemoradiation, 424
IMRT, 424, 425
neoadjuvant therapy, 424
positron emission tomography-directed therapy, 425
screening
barium esophagram, 574
esophageal capsule endoscopy, 574
esophago-gastro-duodenoscopy, 574
methods, 574
recommendations and guidelines, 575
risk factors, 574
squamous cell carcinoma, 574
survival rates, 445
therapeutic prevention, 522, 523
TNM staging, 56
tracheobronchial structures, 445
Esophageal capsule endoscopy (ECE), 574
Esophageal endoscopic resection, 538
Esophageal stenting, esophageal cancer, 351
Esophageal stent placement, 564
Esophagectomy, 59, 60, 424
Esophagogastric junction (EGJ) tumors, 55
Esophago-gastro-duodenoscopy (EGD), 574, 576
Ethanol celiac plexus neurolysis, 354
Etoposide, 638, 672
European Gastro-Intestinal Lymphoma Study Group (EGILS), 333, 338
European Neuroendocrine Tumor Society (ENETS), 271, 278
European Society for Clinical Nutrition and Metabolism (ESPEN), 384
European Society of Medical Oncology (ESMO), 375, 494
European Society of Medical Oncology (ESMO), Magnitude of Clinical Benefit Scale (ESMO-MCBS), 494, 495
EUS fine needle injection (EUS-FNI), 543, 544
EUS-guided biliary drainage, 544
EUS-guided celiac plexus neurolysis (EUS-CPN), 543
EUS-guided tattooing, 544
Everolimus, 88, 619, 625, 672
Excised GI cancer specimens, 33
Exophytic tumors, 22
Exportin 1 (XPO1), 485
Extended lymphadenectomy, 249
Extensive intraoperative peritoneal lavage (EIPL), 81
External beam radiation therapy (EBRT), 422, 423
Extrahepatic cholangiocarcinoma (EHCC), 185
Extrahepatic metastatic disease, 560
Extramural vascular invasion (EVI), 461
Extranodal lymphomas, 333
Extranodal marginal B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type, 330
Extranodal marginal zone B-cell lymphoma (MZL), 49, 331
Extranodal NK/T-cell lymphoma, 335, 337

F
Familial adenomatous polyposis (FAP), 5, 44, 99, 578, 595–597
Familial GIST, 321
Familial pancreatic cancer, 584
Fatigue, 669, 676
Fecal immunochemical tests (FIT), 579
Fecal occult blood testing (FOBT), 579, 580
Fertility preservation
cancer statistics 2017, 633, 634
females
alkylating agents, 635
chemotherapy drugs category, 635, 636
cyclophosphamide-induced gonadotoxicity, 635
cytotoxic drugs, 635, 637
documented counseling, 642
embryo freezing, 642, 643
gonadotropin-releasing hormone agonists, 645
in vitro maturation of oocytes, 645
monoclonal antibodies, 637
oocyte freezing, 643, 644
ovarian tissue cryopreservation, 644
ovarian transposition, 645, 646
TKI, 637
treatment modalities on reproductive organs, impact of, 634, 642
incidence and facts, gastrointestinal cancers, 633, 634
males
assisted ejaculation techniques, 646
chemotherapy drugs, 638
cytotoxic drugs, 638, 639
hormonal analysis, 646
monoclonal antibodies, 639
radiation therapy, 639, 640
semen analysis, 646
sperm cryopreservation, 646, 647
treatment modalities on reproductive organs, impact of, 634, 635
Fibroblast growth factor receptor (FGFR) gene, 191
FGFR2 gene, 201, 619
gene fusions, 623, 624
Fibroblast growth factors (FGFs) signaling, 623
Fibrolamellar hepatocellular carcinoma, 210, 314
carcinoembryonic antigen, 210
differential diagnosis, 211
eosinophilic cells, 211
glandular differentiation with mucin production, 209
hepatic markers, 211
imaging studies, 211
immunohistochemistry, 210
in situ hybridization for al, 210
polygonal cells with abundant eosinophilic cytoplasm, 209
reticulin staining, 211
serum α(alpha)-fetoprotein levels, 210
sinusoidal-like spaces, 210
trabecular patterns with eosinophilic cells, 211
Fibrosarcoma, 47
Fibrosis and hepatic dysfunction, 212
Filiform serrated adenoma, 41
Fine needle aspiration (FNA) biopsy (FNAB), 16, 551
First-Line Advanced Gastric Cancer Study (FLAGS), 83
Flavonols, 512
Flexible fiberoptic endoscopy, 533
Flexible sigmoidoscopy, 579
Flow cytometry, 337
Floxuridine, 561
Fludarabine, 638
Fluorescence in situ hybridization (FISH), 332, 337, 484
5-Fluoro-deoxy-uridine (FUDR), 563
5-Fluorouracil (5-FU)/irinotecan regimens, 140, 166, 602, 635, 638–640, 658, 672, 673, 678
FNA biopsy specimen, 16, 18
Focal nodular hyperplasia, 211
FOLFIRI, 84
FOLFIRINOX (folinic acid [leucovorin], 5-fluorouracil, irinotecan, oxaliplatin) multi-agent chemotherapy, 257, 429, 494
FOLFOX (5-fluorouracil, calcium leucovorin, oxaliplatin), 137, 471, 561, 637, 638
FOLFOX4, 640
FOLFOXIRI, 141
Follicular lymphoid hyperplasia, 336

Follicular lymphoma (FL), 49, 338, 341
Follicular lymphoma-specific International Prognostic Index (FLIPI), 344
Foregut carcinoids, 273
Foregut tumors, 270
Four-dimensional CT (4DCT) imaging, 421
4-point grading system, 52
FRAGEM trial, 373
Fruit and vegetable consumption, 7
Functional Assessment of Cancer Therapy-Fatigue Scale (FACT-F), 676
Functional pancreatic NETs, 277
Function preserving surgery, 81
Fundus down technique, 406
Future liver remnant (FLR), 556

G
Gallbladder cancer (GBC), 434
  diagnostic biomarkers, 198
  epidemiology, 4
  intrahepatic vs. extrahepatic cholangiocarcinoma, 199
  ongoing trials, 201, 202
  pathogenesis, 197, 198
  risk factors, 197
  survival, 197
  targeted therapies
    EGFR inhibitors, 200
    FGFR2 inhibitors, 201
    HER2 inhibitors, 200
    MET inhibitors, 201
    PI3K-AKT-mTOR pathway, 201
    RAS-RAF-MEK-MAPK pathway, 201
    VEGF inhibitors, 200, 201
  treatment
    locally advanced disease, 199
    metastatic disease, 199
    resectable disease, 198, 199
    unresectable disease, 199
Gallbladder polyps, 197
Gastrectomy with D2 lymphadenectomy peritoneal recurrence, 413
Gastric adenocarcinoma (GAC), 447
  accurate staging, 447
  endoscopy, 447
  imaging
    computed tomography, 447–449
    MRI, 449, 450
    PET-CT, 450
  morphologic appearances of, 447
  survival rates, 447
Gastric adenoma, 75
Gastric cancer (GC), 617, 658
  adjuvant treatment
    adjuvant chemoradiotherapy, 81, 82
    adjuvant chemotherapy, 82, 83
    perioperative/neoadjuvant chemotherapy, 82
  age-standardized mortality rate, 2
  atrophy/intestinal metaplasia, 73
  charged particle therapy, 428
  in children, 316
  diagnosis, 76
  early gastric cancer, 77
  environmental factors, 73
  epidemiology, 2, 368
  epigenetic alterations, 73
  Helicobacter pylori infection, 2
  histological types, 2
  histopathologic evaluation, 76
  immunotherapy
    CTLA-4 inhibitor, 89
    PD-1/PD-L1 Inhibitor, 90
  IMRT, 427, 428
  incidence, 2, 73, 368, 575
  Intergroup/SWOG trial, 427
  LADG vs. ODG, 79, 80
  MAGIC trial, 427
  in males, 2
  molecular analysis, clinical utility of
    FGFR2, 619
    HER2 inhibitors, 618, 619
    immune checkpoint inhibitors, 618
    PI3K-AKT-mTOR inhibitors, 619
    vascular endothelial growth factor receptor blockade, 619
  molecular classification, 75–76, 617, 618
  p53, 73
  palliative chemotherapy
    AKT/mTOR, 88
    cancer stem cell, 89
    cytotoxic chemotherapy, 83, 84
    epidermal growth factor receptor, 86, 87
    FGFR, 88
    HER2, 84, 85
    MET, 87
    PARP, 88, 89
    second-line chemotherapy, 84
    VEGFR2, 85, 86
  palliative gastrectomy vs. non-operative management, 352
  pathology
    advanced carcinoma, 74
    early cancer, 74
    esophago-gastric junction, 74
    hereditary diffuse gastric cancer, 75
    indeterminate type, 74
    lymph node involvement, 74
    mixed adenoneuroendocrine carcinoma, 74
    mixed type, 74
    neuroendocrine carcinoma, 74, 75
    papillary/tubular carcinoma, 74
  peritoneal dissemination, 413
  population-based screening, 76, 576
  prevalence, 73
  risk factors, 74
  screening
    esophago-gastro-duodenoscopy, 576
    population-based screening, 576
    recommendations and guidelines, 577
    risk factors, 575, 576
    serological testing, 576, 577
    X-ray photofluorography, 576
  staging workup, 76
  surgery
    function preserving surgery, 81
    lymphadenectomy, 77–79
    minimally invasive surgery, 79, 80
    reduction surgery, 80, 81
    robot-assisted surgery, 81
  survival rates, 2
  therapeutic prevention, 523, 524
  virulence factors, 73
Gastric carcinoids, type I and II, 276
Gastric gastrointestinal stromal tumor (GIST), 449
  with KIT/PDGFR mutation, 322

Gastric intestinal metaplasia (GIM), 523, 575
Gastric lymphoma, 448, 449
  bone marrow biopsy and aspirate, 332
  chemoimmunotherapy, 334
  combination chemoimmunotherapy, 334
  diagnosis, 331, 332
  distribution, 330
  endoscopic and imaging findings, 331
  endoscopic ultrasound-guided fine needle aspiration biopsy, 331
  epidemiology, 330
  etiology, 330
  fertility-preserving measures, 332
  follow-up, 334, 335
  histological evaluation of repeat biopsies, 334
  histopathological and immunohistochemical examination, 331
  immunophenotyping, 331
  immunosuppressive therapy, 330
  immunotherapy-based treatment, 334
  incidence, 330
  long-term immunosuppressive therapy, 330
  molecular diagnostic analysis, 331
  normal-appearing mucosa, 331
  positron emission tomography, 332
  predisposing factors, 330
  radiation therapy, 334
  risk factors, 330
  rituximab to anthracycline-based combination therapy, 334
  stage and histological grade, 333
  staging
    bone marrow biopsy, 332
    clinical parameters, 332
    computed tomography, 332
    endoscopic ultrasonography, 332
    physical examination, 332
    positron emission tomography, 332
    prognostic stratification, 332
  superficial spreading/diffuse infiltrating lesions, 331
  suspicious-appearing lesions, 331
  treatment, 333, 334
Gastric outlet obstruction (GOO), 405, 544, 545
Gastric peritoneal carcinomastosis (GPC), 413
  advanced nodal status, 413
  advanced T stage, 413
  diffuse mixed histology, 413
  HIPEC, 413
  occurrence, 413
  peritoneal lavage specimens, 413
  risk factors, 413
  signet ring cell histology, 413
  systemic chemotherapy, 413
  therapeutic HIPEC, 413
  traumatic release from surgical manipulation, 413
  tumor size, 413
Gastric type adenocarcinoma, 75
Gastrinomas (Zollinger-Ellison syndrome), 270
Gastroduodenal stenting (GDS), 565
Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), 277
  anatomic locations, 270
  asymptomatic stage lesions, 270
  cisplatin vs. carboplatin plus etoposide, 282
  classification and nomenclature, 270
  colonoscopy screening, 270
  cytotoxic chemotherapies
    decarbazine, 281
    oxaliplatin-containing regimens, 281
    streptozocin combination with fluorouracil, 281
    temozolomide, 281
  detection rates, 270
  enterochromaffin (neuroendocrine) cells, 270
  fluorouracil plus leucovorin efficacy, 282
  high-grade/poorly differentiated, 270
  high tumor grade, 283
  incidence, 269, 270
  irinotecan, 282
  molecular analysis, clinical utility of, 625
  molecular classification, 624, 625
  NANETS and ENETS guidelines, 282
  nomenclature and classification, 270
  paclitaxel to platinum plus etoposide, 282
  platinum-based chemotherapy, 282
  platinum (cisplatin) plus etoposide regimens, 282, 283
  poorly differentiated histology, 283
  proliferative rate, 270
  second-line therapy, 282
  SEER analysis, 270
  site-specific classification, 270
  somatostatin-analogs, 283
  temozolomide-based treatment, 282
  topotecan, 282
  toxic chemotherapy, 282
  well-differentiated neuroendocrine tumors, 270
Gastroesophageal reflux disease (GERD), 55, 574, 575
Gastrointestinal and pancreatic NETs, histologic evaluation, 277
Gastrointestinal cancer prevention
  in children, 311
  current management guidelines, 509, 511
  diet
    colorectal cancer, 511–513
    non-colorectal gastrointestinal tumors, 513
  genetic model for colorectal carcinogenesis, 509, 510
  lifestyle factors
    obesity, control of, 515, 516
    physical activity (*see* Physical activity)
  premalignant conditions of, 509, 511
  primary prevention, 510
  secondary prevention, 510
  tertiary prevention, 511
  therapeutic prevention
    anal cancer, 521
    colorectal cancer, 517–521
    esophageal cancer, 522, 523
    gastric cancer, 523, 524
    hepatobiliary cancer, 524
    pancreas cancer, 524
Gastrointestinal decompression, 671
Gastrointestinal (GI) lymphomas
  in children
    bone marrow aspiration and biopsy, 315
    chemotherapy, 316
    clinical presentation, 315
    complete blood count, 315
    contrast enhanced CT imaging, 315
    epidemiology, 315
    polychemotherapy, 316
    positron emission tomography, 315
    staging, 315
    treatment approaches, 316
    tumor histology, 315
  histologic subtypes, 329
  nodal disease, 329
  pretreatment evaluation, 330

risk factors, 329
staging system, 329
treatment, 329
Gastrointestinal (GI) malignancies
adjuvant and neoadjuvant therapies, 351
anxiety disorders, 359
chemotherapy and biological therapies, 351, 361
clinical urgency, 360, 361
depression, 359
emotional and psychological effects, 359
management, 351
medical care, 361
pain management
abdominal pain, bowel obstruction, 355
causes, 355
celiac plexus block, 354
celiac plexus involvement, primary/metastatic disease, 355
celiac plexus neurolytic block, 354
central nervous system toxicity, 355
chemotherapy strategies, 355
clonidine, 355
control of, 354
curative-intent surgery, 354
fentanyl, 355
intercostal nerve involvement, 355
intrathecal infusion of morphine, 356
intrathecal infusion pumps, 355, 356
local anesthetics, 355
morphine and hydromorphone, 355, 356
neuropathic pain, 355
nociceptive pain, 355
opioid therapy, 355
paracentesis, 355
pelvic recurrences, 355
primary/metastatic tumors, 355
radiation therapy, 355
renal/hepatic compromise, 355
sacral plexus involvement, pelvic recurrence of disease, 355
spinal cord compression, 355
palliative care, 351–354 (*see* Palliative care, GI malignancies)
pathological evaluation of biopsy material, 359
patient-centered care, 361
patient readiness and clinical urgency, 361
patient's quality of life, 361
PHQ-9, 359
platinum-induced neurotoxicity, 356, 357
prognosis, 359–361
recurrence, 351
religious coping characteristics, 362
standard care vs. communication strategy, 362
Gastrointestinal neuroendocrine tumors, classification, 319
Gastrointestinal stenting, 563
colonic stenting, 565, 566
for esophageal obstruction, 563–565
gastroduodenal stenting, 565
Gastrointestinal stromal tumor (GIST), 16, 48, 49, 289, 448, 454, 455, 614, 637
anatomic considerations, 295
asymptomatic, 289
chemotherapy, 294
in children
clinical presentation, 321
diagnosis/staging, 322
epidemiology, 321
gastrointestinal bleeding, 321
histologic patterns, 321
mitotic index and size, 322
outcomes, 322
pathogenesis, 321
risk factors, 321
treatment, 322
tumor predisposition syndromes, 321
tumor rupture, 322
clinical behaviors, 293
clinical trials, 302
contrast-enhanced CT scan, 290
crenolanib, 302
CT evidence of response, 290
cytoreductive surgery, 300
dasatinib, 302
disease-free survival, 294
endoscopic ultrasound, 290
etiology, 293
histologic evaluation, 290
imatinib, 294
adjuvant treatment, 296, 297
adverse events, 299
BFR14 study, 299
B-2222 study, 298
cardiotoxicity, 299
clinical trials, 296
computed tomography scan, 291
CYP450 3A4, 299
dosing and duration, 298–299
enzymatic pathway, 299
epithelioid features, 292
hypodense tumor, 300
intratumoral hemorrhage/degeneration, 299
mutational status, 299
neoadjuvant imatinib, 297, 298
primary resistance, 300
prospective clinical trials, 298
secondary resistance, 300
side effects, 299
supportive care, 299
treatment algorithm, 295
tumor density, 299
immunohistochemical staining for KIT, 290
immunotherapy, 303
incidence, 290
KIT gene mutations, 292
laparotomy, 295
magnetic resonance imaging, 290
masitinib, 302
metastasectomy, 300
metastases, 289
minimally invasive surgery, 295
molecular abnormalities, 289
molecular analysis, 290
molecular classification, 292, 293
mutations in, 294
neoadjuvant imatinib, 296
nilotinib, 302
nomogram, 293, 294
NTRK fusions, 302
ponatinib, 302
positron emission tomography, 290
prognostic factor, 293
recurrence, 293
recurrence-free survival, 294
regorafenib, 301
resection of residual disease, 300

Gastrointestinal stromal tumor (GIST) (*cont.*)
risk of recurrence/metastases, 294
sorafenib, 302
sporadic, 293
subepithelial mass on endoscopy, 290
submucosal tumors, 289
sunitinib, 300, 301
surgery goals, 294
symptomatic patients, 289
TKI therapy, 301
translational therapeutics in oncology, 289
treatment algorithm, 294
tumor characteristics, 293
tumor rupture, 294
tumor size and mitotic rate, 293
tyrosine kinase inhibitor therapy, 294
unresectable liver metastases, 300
vatalanib, 302
Gastrointestinal subepithelial lesions, biopsy of, 535
Gastrointestinal subepithelial tumors, endoscopic management of, 540
Gastrointestinal system (GIS) malignancies, in children, *see* Pediatric GIS cancers
Gastrointestinal toxicity, 673
Gastrointestinal tract by systemic lymphomas, extranodal involvement
activated B-cell subtype, 344
bendamustine/rituximab, 345
centroblasts, 343
chemotherapy, 345
clinical manifestations, 341
cytological variants of MCL, 343
diagnosis, 342, 343
endoscopy and colonoscopy, 344
epidemiology, 341, 342
etiology and risk factors, 342
extranodal disease, 343
follow-up, 345
ibrutinib, 345
laboratory studies, 343
maintenance rituximab therapy, 344
neutropenic fever, 344
NF-κ (kappa)B pathway, 344
nodal enlargement, 341
prognostic factors, 341, 344
R-CHOP, 344
reference hematopathology laboratory, 342
R-HyperCVAD with high-dose cytarabine and methotrexate, 344
rituximab-based chemotherapy, 344
secondary extranodal involvement, 341
site-related symptoms, 341
staging, 343, 344
subtypes, 341
surgical intervention, 344
systemic chemotherapy plus rituximab, 344
treatment, 344, 345
Gastroparesis, 671
Gastrostomy tubes, 388
GATSBY trial, 85
Gela score, 334
Gemcitabine, 428–431, 433, 434, 639, 658, 672, 678
Gemcitabine, docetaxel and capecitabine (GTX), 429
Gemcitabine nab-paclitaxel, 257
Gene fusions, 614, 615
Gene mutation testing, 137
Genetic counseling, 603, 604
Genetic exceptionalism, 604
Genetic polymorphisms of UGT1A1, 358
Genomic profiling, 616, 622
Genomic sequencing, 614
German CONKO-003 trial, 257
Germinal epithelium, 635
Germline mutations in *BRCA2*, 482
GITSG trial, 239, 240
Glisson's capsule, 406
Glucocorticoid-induced TNFR-related protein (GITR), 472
Glycopyrrolate, 671
Goblet cell carcinoids (GCC)
atypical, 103
clinical presentation, 103
diagnosis, 103
localized early stage disease, 104
locally advanced and metastatic disease, 104
prognosis, 104
staging system, 104
Gonadal function preservation, 633
Gonadal shielding, 647
Gonadotropin-releasing hormone agonists (GnRHa), 645
Graft-versus-host disease (GVHD), 663
Granulocyte macrophage colony-stimulating factor (GM-CSF), 469
Group sequential methods, 503
Guaiac-fecal occult blood testing (gFOBT), 579, 580
GVAX pancreas vaccine, 261
GVAX with cyclophosphamide and CRS-207, 263
Gynecologic surveillance, 605

H
Haemophilus influenzae type b (Hib) vaccination, 665
Haloperidol, 671
HCC, *see* Hepatocellular carcinoma (HCC)
Heat-sink effect in hypervascular tumors, 217
Heavy particle therapy, 423
Hedgehog (HH) and Notch signaling cascade, 260, 481, 482
Helicobacter pylori, 6, 7
antibody screening, 577
eradication therapy, 334
infections, 2, 330
Hematological complications, 677
Hematopoietic cell transplantation (HCT), 339
Hematopoietic stem cell transplantation (HSCT), 663
HepaSphere, 561
Hepatic arterial infusion (HAI) therapy, 143
Hepatic jaundice, 675
Hepatic metastasectomy, 142
Hepatic parenchyma, 406
Hepatic resection, 556
Hepatic reserve assessment, 212
Hepatic tumors, in children
benign/malignant, 311
blastemal origin, 312–314
epithelial origin, 314, 315
Hepatic ultrasound, 583
Hepatitis A vaccination, 666
Hepatitis B vaccination, 666
Hepatitis B virus (HBV), 6, 314, 524
Hepatitis C virus (HCV) infection, 6, 314, 524
Hepatobiliary cancer
epidemiology, 368
therapeutic prevention, 524
Hepatoblastoma
children
clinical presentation, 312
diagnosis, 312
epidemiology, 312
histopathological subgroups, 312

outcomes, 314
prognostic factors, 312
staging system, 312
treatment, 312–314
risk groups stratification, 312
Hepatocellular carcinoma (HCC), 4, 50, 513, 524, 558, 560, 581
adult type and variants, 314
anatomic resection, 213, 214
vs. nonanatomic resection, 213
asymptomatic, 207
cancer mortality, 207
children
arterial phase hypervascularization, 314
chemotherapy, 315
clinical presentation, 314
diagnosis, 314
epidemiology, 314
histopathological subtypes, 314
overall survival rate, 315
prognosis, 315
radiological investigations, 314
treatment, 315
chronic hepatitis B virus infection, 207
cirrhosis, 207
clinical trials, 224–225
epidemiology, 368
functional single-photon emission CT with technetium-99m sulfur colloid, 222
grading, 211
hepatic resection, 212
hepatic transarterial embolization, 215–217
histopathology
bile ducts, 207
clear-cell variant, 208
definitive hepatocellular differentiation, 208
diagnosis, 208
encapsulated, 207
extrahepatic metastasis, 207
hyaline bodies, 209
immunohistochemical/ultrastructural studies, 208
intracytoplasmic inclusions, 208
light microscopy, 208
multifocal, 207
nodular mass, 207
pedunculated tumor, 207
portal and hepatic veins and vena cava, 207
pseudocapsule, 207
reticulin staining, 208
single nodule, 207
special stains, 208
undifferentiated carcinoma, 209
with hyaline globules, 210
incidence of, 581
international normalized ratio, 368
interventional radiology, 215
intrahepatic recurrence, 213, 214
intraoperative consideration, 214
MET signaling, 227
with microvascular invasion, 214, 215
mitogen-activated protein kinase kinase tyrosine kinase activity, 227
molecular analysis, clinical utility, 623
cabozantinib, 623
fibroblast growth factor signaling, 623
pembrolizumab, 623
molecular classification, 623
molecularly targeted therapy
axitinib, 226
bevacizumab, 226
brivanib, 226, 227
everolimus, 227
immune checkpoints, 227
immunotherapies, 227
mammalian target of rapamycin, 227
microvascular density, 224
nivolumab, 227
preclinical and clinical studies, 224
regorafenib, 226
sorafenib, 226
sunitinib, 226
tremelimumab, 227
tumor expression of PD-L1, 227
multicentric carcinogenesis, 213
nonanatomic resection, 213
non-preventable risk factors, 207
nontumoral hepatic parenchyma, 213
particle therapy, 432, 433
pathologic staging, 211
patient selection and pathologic factors, 212
preventable risk factors, 207
prognostic factors, 214, 215
radiotherapy, role of, 219–221
RAS/RAF/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathway, 227
recurrence-free survival rates, 214
risk factors, 207
SBRT, 431, 432
screening
alcoholic liver disease, 582
chronic hepatitis B, 581, 582
chronic hepatitis C, 582
cirrhosis, 582
diagnostic algorithm for, 583
evidence of benefit, 583
high-risk population, 581
radiological tests, 583
screening interval, 583
serological tests, 582
staging, 211
surgical resection, 213, 214
survival benefit, 215
treatment
5-fluorouracil, 223
chemotherapeutic regimens, 223
cisplatin, 223
combinations of chemotherapeutic agents, 223
capecitabine and cisplatin, 223
cisplatin, interferon α(alpha)-2b, doxorubicin, and 5-fluorouracil, 223
epirubicin, cisplatinum and infusional 5-fluorouracil, 223
gemcitabine and doxorubicin, 223
gemcitabine and oxaliplatin, 223
oxaliplatin, 5-fluorouracil and leucovorin, 223
gemcitabine, 223
molecularly targeted therapy, 223, 224
nonsurgical therapies, 222
preclinical trials, 223
single-agent chemotherapies, 223
staging and prognostic systems, 222
supportive care, 222
surgical, 222
systemic chemotherapy, 222
vascular invasion, 213, 215

Hepatocyte growth factor (HGF), 87
Hereditary breast and ovarian cancer (HBOC) syndrome, 5, 6, 617
Hereditary diffuse gastric cancer (HDGC), 75, 576, 607, 617
Hereditary gastric cancer, 607, 609, 610
Hereditary gastrointestinal cancer for medical oncologist
  familial adenomatous polyposis, 595–597
  hereditary gastric cancer, 607, 609, 610
  hereditary nonpolyposis colon cancer (*see* Hereditary nonpolyposis colon cancer)
  hereditary pancreatic cancer, 610
  polyposis syndromes
    juvenile polyposis, 606, 607
    Peutz-Jegher syndrome, 605, 606
Hereditary nonpolyposis colon cancer, 44, 578, 597
  Bethesda guidelines, 600, 601
  clinical decision-making, 600
  clinical surveillance and practice guidelines, 604
  early working groups, 598
  genetic counseling and testing in at-risk relatives, 603, 604
  genetic counselors, testing algorithms and operational issues for, 601, 602
  genotype/phenotype correlations, 598, 599
  gynecologic surveillance, 605
  IHC, 600
  microsatellite instability, 599, 602, 603
    in tumors, 598
  mismatch repair gene mutations, 598
  pathology, 598
  predictive models, 601
  terminology, problems of, 597, 598
  universal testing, 601
  upper gastrointestinal tract surveillance, 605
Hereditary non-polyposis colorectal cancer (HNPCC), *see* Lynch syndrome. *See* Lynch syndrome
Hereditary pancreatic cancer, 610
Hereditary polyposis syndromes, 99
Hereditary syndromes, colorectal cancer
  Cronkhite-Canada syndrome, 46
  familial adenomatous polyposis, 44
  HNPCC/Lynch syndrome, 44
  Juvenile polyposis syndrome, 45
  MutY-associated polyposis, 44
  Peutz-Jegher syndrome, 46
  serrated polyps, 44
Heterotopic transplantation, 644
High-dose-rate brachytherapy (HDR-IORT), 423
High-grade dysplasia (HGD), 540, 576
High-grade neoplasms, 412
High-grade squamous cell intraepithelial lesions (HSIL), 177, 178
High-level immunosuppressed patients, 663
Highly active anti-retroviral therapy (HAART), 181
Highly emetogenic chemotherapy, 673
High microsatellite instability (MSI-H), 620
High-risk genetic syndromes, 578
Hilar cholangiocarcinoma, 553
Hindgut tumors, 271
Histogenetic classification, 27
Histone deacetylase (HDAC), 625
HMG-CoA reductase inhibitors (statins), 519
Hodgkin's lymphoma, 50
Home parenteral nutritional support, 390
Homologous recombination (HR), 615
HPV-related precancerous high-grade anal intraepithelial neoplasia (HGAIN), 175
Human epidermal growth factor receptor (HER)
  HER2 amplification, 84, 85, 190, 621
  HER2 antagonists, 155–156
  HER2 inhibitors, 200, 618, 619
  HER1 pathway, 480
  HER2 pathway, 480
Human equilibrative nucleoside transporter 1 (hENT1), 263
Human genome project, 613
Human HER2-positive gastric cancer xenograft model, 85
Human immunodeficiency virus (HIV) infection, 175, 330
Human microbiome studies, 7
Human papilloma virus (HPV), 175
  vaccination, 666
Hyaluronan, 260, 263
Hydrodissection, 556
Hyoscine butylbromide, 671
Hypergastrinemia, 276
Hyperplastic polyps (HPs), 39, 40
Hyperthermia-induced, myocardial oxygen demand, 401
Hyperthermic intraperitoneal chemotherapy (HIPEC), 675
  chemoperfusant, 410
  closed technique, 409
  drug metabolism, 411
  drugs, intraperitoneal drug concentration and exposure, 411
  drug toxicities, 410
  inflow and outflow catheters, 409
  intraperitoneal route, 410
  membrane permeability, 411
  microscopic in situ malignant cells, 409
  mitomycin C, 411
  patient selection and therapy guidelines, 409
  perfusate fluid, 411
  perfusion cannulas, 409
  peritoneal cavity expander, 409
  peritoneal-plasma barrier, 410
  peritoneum-tumor barrier, 409
  variability, 409
Hypocellular biopsy tissue material, 534
Hypofractionated approach, 425
Hypofractionated proton beam therapy, 434
Hypoxia-activated agents, 259, 260

I

IDH1/2 mutations, 624
Ifosfamide, 638
Ileal lymphoma, 456
Image-guided biopsy for diagnosis, 551, 552
Image-guided locoregional therapies (LRTs), HCC, 215
Imatinib, 613, 658, 672
Immune checkpoints, 262
  inhibitors, 89, 192, 262, 263, 618, 624
Immune escape, 465, 466
Immune-related response criteria (irRC), 497
Immune surveillance, 465
Immune therapy, cancers, 261
Immunodeficiency, 330
Immunoediting, 465
Immunohistochemistry (IHC), 21, 22, 600
  and molecular studies, small intestinal lymphomas, 337
Immunomarkers, 22
Immunonutrition, 386, 387
Immunophenotyping, 21, 337
  MCL, 343
Immunoproliferative small intestinal disease (IPSID), 335
Immunosuppression, degree of, 663
Immunotherapy, 154, 155

biliary tract cancer, 192
CTLA-4 inhibitor, 89
IMRT, *see* Intensity-modulated radiation therapy (IMRT)
Inactivated polio vaccine (IPV), 666
Inclusive peritonectomy, 406
Incomplete cytoreduction, 400
Independent data monitoring committee (IDMC), 493, 503
Indolent lymphomas of small intestine, 338
Infiltrative ulcerating tumors, 22
Inflammatory state, 8
Influenza vaccination, 664
Inherited bone marrow failure syndromes, 316
Inherited disorders associated with pancreatobiliary neuroendocrine tumors, 272
Innate immunity
macrophages, 466, 467
natural killer T, 466
INNOVATION trial, 502
Innovative biomarker-driven phase II trials, 501
basket trials, 501, 502
umbrella trials, 502
Inoperable pancreatic cancer, 565
In-situ hybridization (FISH and CISH), 21
Insulin-like growth factor 1 receptor (IGF1R), 258, 482
Insulinomas, 320
Intense lymphocytic intretumoral infiltrates, 43
Intensity modulated proton therapy (IMPT), 425, 426
Intensity modulated radiation therapy (IMRT), 421, 422, 426, 438, 641
in anal cancer, 437, 438
in esophageal cancer, 424, 425
gastric cancer, 427, 428
in pancreatic cancer, 428
in rectal cancer, 435
Tungsten metal leaves, 422
Intensive dietary counseling, 389
Interferon alpha (IFNa), NETs, 278
International Agency for Research on Cancer (IARC), 5
International Childhood Liver Tumor Strategy Group, 312
International Extranodal Lymphoma Group (IELSG) on gastric lymphoma, 334
International normalized ratio (INR), 212
International Prognostic Index, 343
International Society for Fertility Preservation (ISFP), 642
International Society on Thrombosis and Haemostasis (ISTH) criteria, 373
Interventional endoscopic ultrasound
EUS fine needle injection, 543, 544
EUS-guided biliary drainage, 544
EUS-guided celiac plexus neurolysis, 543
Interventional oncology (IO), 551
Interventional radiology (IR)
biliary interventional, 552
celiac neurolysis, 567
gastrointestinal stenting, 563
colonic stenting, 565, 566
for esophageal obstruction, 563–565
gastroduodenal stenting, 565
self-expandable metal stents, 563
hydrodissection, 556
image-guided biopsy for diagnosis, 551, 552
percutaneous ablative therapies, 553
cryoablation, 554
hydrodissection and patient positioning, 553
irreversible electroporation, 554–556
microwave ablation, 554, 555
radiofrequency ablation, 553, 554
percutaneous gastrostomy, 566, 567
portal vein embolization, 556–558
transarterial treatment of liver tumors
selective internal radiotherapy with Y-90, 561–563
transarterial chemoembolization (*see* Transarterial chemoembolization (TACE))
urinary obstruction, 552, 553
Intestinal metaplasia, 575
Intestinal obstruction, 674
Intestinal T-cell lymphoma (ITL), 335
Intraarterial hepatic chemoembolization (IAHC), 563
Intraductal papillary mucinous neoplasms (IPMN), 317, 524, 535, 585
Intraepithelial neoplasia (IEN), 509
Intrahepatic cholangiocarcinoma (IHCC), 185, 220
Intramucosal carcinoma, 40
Intraoperative radiation therapy (IORT), 423
Intraperitoneal chemotherapy (IPC), 81
Intraperitoneal disease, 104
Intra-tumoral lymphocytes and mucinous differentiation, 607
Intrauterine growth restriction (IUGR), 658
Intravascular lymphoma (IVL), 50, 332
Invasive lobular carcinoma, 609
In vitro fertilization (IVF), 642
In vitro maturation (IVM), 643
of oocytes, 645
Ipatasertib (GDC-0068), 88
Ipilimumab, 89, 471
Irinotecan, 558, 620, 635, 637–639, 658, 672, 673, 678
Irinotecan-induced diarrhea, 357, 358
Irradiated healthy liver volume, 219
irRECIST criteria, 497
Irreversible electroporation (IRE), 554–556
Islet cell tumors, 269
Isocitrate dehydrogenase (IDH) 1/2, 191

J
JACOB study, 85
Janus kinase (JAK) pathway, 260
Jaundice, 675, 676
JCOG9912 study, 83
Jejunosotomy (J) tubes, 388
Juvenile polyposis syndrome (JPS), 45, 606, 607

K
Kaposi sarcoma (KS), 47, 48
KEYNOTE-012 phase Ib study, 90
Khorana score, 372, 373
Ki67 (MIB1) index, 19
Korean Laparoscopic Gastrointestinal Surgery Study Group (KLASS), 79
KRAS mutations, 371, 474, 480, 481, 622
and *BRAF* mutational testing, 43, 44

L
Lactic dehydrogenase (LDH), 343
Lanreotide, NETs, 278
Laparoscopic-assisted distal gastrectomy (LADG), 79
Laparoscopy, 659
Laparoscopy-assisted PPG (LAPPG), 81
Lapatinib, 621
Large circumferential jejunal ulcers without overt tumor masses, 337
Large polyps, 38
Larotrectinib, 621

Late-onset diarrhea of irinotecan, 358
Lauren classification, 28
Lauren's criteria, 74
Leeds Castle Polyposis Group (LCPG), 598
Leiomyosarcomas, 47, 48
Lenvatinib, 623
Leucovorin, 640
Leydig cells, 635, 641
Li-Fraumeni syndrome, 575, 597
Linitis plastica, 447, 448
Lipiodol, 558
Lipogenesis, 380
Lipoleiomyosarcomas, 47
Lipolysis, 380
Liposomal delivery system, 483, 484
Liposomal irinotecan, 485
Liquid biopsy, 625
Liver cancers, image-guidance techniques, 220
Liver-directed therapy, 143–144
Liver failure, tumor replacement, 276
Liver insufficiency, 556
Liver transplantation, 277, 314, 320
  and arterial chemoembolization, 314
Liver tumor tracking, 219
Liver volumetry and portal vein embolization, 212, 213
Locally advanced disease
  definitive chemoradiotherapy, 61
  neoadjuvant treatment, 61–63
  non-operative treatment, 63, 64
Locally advanced pancreatic cancer (LAPC), 428–431
Locoregional therapies, HCC
  advanced stage, 218, 219
  early stage, 217, 218
  intermediate stage, 218
  very early stage, 217
LOGiC trial, 85
Lomustine, 638
Lorazepam, 672, 673
Low emetogenic chemotherapy, 673
Low-grade anal intraepithelial neoplasia (LGAIN), 177
Low-grade and high-grade appendiceal mucinous neoplasms, 412
Low-grade appendiceal mucinous neoplasms (LAMN) (classic pseudomyxoma peritonei) or peritoneal mesothelioma, 400, 412
Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue, 331
Low-grade dysplasia (LGD), 540, 541, 576
Low-grade squamous cell intraepithelial lesions (LSIL), 177
Low-level immunosuppression, 663
Low malignant potential (LMP) tumors, 416
Low-molecular weight heparin (LMWH) monotherapy, 677
Lugano classification, 338
Lugano staging system, 332, 337
Lugano system, 332, 338
  for staging of gastrointestinal lymphomas, 333
Luminal obstruction, 411
Lung NETs/bronchial carcinoids, 271
Lymphadenectomy, 77–79, 249
Lymphatic invasion by tumor, 33
Lymph node metastasis, 52
Lymphocyte activation gene-3 (LAG-3), 472
Lymphoepithelioma-like carcinoma, 209
Lymphoid infiltrate in post-treatment gastric biopsies, 334
Lymphoma
  Burkitt lymphoma, 50
  diffuse large B cell lymphoma, 49
  extranodal marginal zone lymphoma, 49
  follicular lymphoma, 49
  Hodgkin's lymphoma, 50
  incidence, 315
  intravascular lymphoma, 50
  primary effusion lymphoma, 50
  T-cell lymphoma, 50
Lymphoma malign B (LMB-96), 316
Lymphomatoid granulomatosis, 332
Lymphomatous in peritoneum, 453
Lymphomatous submucosal nodules producing polypoid lesions, 341
Lynch syndrome, 5, 44, 471, 578, 617
  See also Hereditary nonpolyposis colon cancer

M

99mTc Macro-aggregated albumin (MAA), 563
Macrophages, 260, 261, 466, 467
Macroscopic classification, 22–24
MACRO-TTD trial, 146
Magnetic resonance cholangiopancreatography (MRCP), 610
Magnetic resonance colonography (MRC), colon cancers, 461, 462
Magnetic resonance imaging (MRI)
  colorectal cancers, 457
  gastric adenocarcinoma, 449, 450
  peritoneal carcinomatosis, 452, 453
  pregnancy, 657
  rectal cancers, 458, 461
  small bowel, malignant disease of, 456, 457
Magnetic resonance pancreatography (MRP), 605
Maintenance therapy
  bevacizumab and combinations, 145–148
  chemotherapy-free interval, 145
  definition, 144
  EGFR inhibitors, 148
  intermittent irinotecan, 146
  leucovorin/5-FU therapy, 145
    without oxaliplatin, 145
    with/without bevacizumab, 144
  optimal duration, 144
  OPTIMOX1 study, 145
  OPTIMOX2 trial, 145
  oxaliplatin, 144
  stop-and-go strategies, 144
Major histocompatibility complex (MHC) class 1 molecules, 466
Malignant adenoma, 41, 42
Malignant ascites, 675
Malignant biliary obstruction (MBO), 552
Malignant bowel obstruction (MBO), 674, 675
  abdominal radiographs, 352
  advanced intra-abdominal malignancy, 352
  algorithm, 353
  corticosteroids, 353
  decision-making, 353
  dexamethasone's mechanism of action, 353
  end-of-life care, 352
  fecal stasis, 352
  histamine 2 antagonists, 354
  malignant adhesions, 352
  management, 352–354
  medical management, 354
  medical treatment, 353
  morbidity and mortality, 352
  obstruction, 352
  octreotide therapy/surgical management, 352, 353
  PEG placement, 354

proton pump inhibitors, 354
ranitidine, 353
risk factors, 353
surgical intervention, 353
Malignant carcinoid syndrome, 674
Malignant esophageal obstruction, 544
Malignant peritoneal mesothelioma (MPM), 415
Malignant polyps, 42
Malnutrition, 379, 566, 670, 676
adverse outcomes, 383
anthropometric measurements, 384
assessment methods, 383
body composition measurements, 384
1-3 day dietary record, 384
detection and prevention, 383
5-fluorouracil, 384
laboratory parameters, 384
low subcutaneous and muscular fat, 384
morbidity and mortality, 383
numerical score, 383
nutritional assessment tools, 384
phase angle, 384
prolonged hospital stay, 383
screening/assessment, 383–384
visual analog score, 383
weight loss during treatment, 379, 383
Malnutrition universal screening tool (MUST), 384
MALT lymphoma-associated translocation (MALT1) protein, 330, 331, 335
of colorectal region, 340
Mammalian Target of Rapamycin (mTOR) pathway, NETs, 278
Mantle cell lymphoma (MCL), 339, 341
Maximum tolerated dose (MTD), 499, 500
MD Anderson Cancer Center (MDACC), 236
Measles, mumps, rubella (MMR) vaccination, 665
Mechlorethamine, 638
Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, 427
Megestrol acetate, 676
MEK and PI3K/AKT pathways, 258
MEK inhibitor trametinib and everolimus (mTOR inhibitor), 259
Melanoma, 51
MELD score, 212
Melphalan, 638
Meningococcal vaccination, 666
MEN-1 syndrome, 276
Mercaptopurine, 663
6-Mercaptopurine (6-MP), 638
Mesenteric carcinoid tumor, 452
Mesenteric desmoplastic fibrosis, 274
Mesothelioma, 50
MET inhibitors, 201
Metabolic pathways, 622
Metachronous lesions, 59
Metagenomics approaches, 7
Metastatic adenocarcinoma, 255
Metastatic breast carcinoma, 50
Metastatic clear-cell renal cell carcinoma, 211
Metastatic colo cancer, irinotecan, 357, 358
Metastatic colorectal cancer (mCRC), 493, 496, 558
BRAF inhibition, 155
chemotherapy options
combined with VEGF and EGFR inhibitors, 142
FOLFIRI combined with VEGF or EGFR inhibitors, 140–141
FOLFOX, 137
FOLFOX combined with EGFR inhibitors, 138, 139
FOLFOX combined with VEGF inhibitors, 138
FOLFOXIRI, 141
FOLFOXIRI combined with bevacizumab, 141, 142
IFL, 139
XELOX, 139
XELOX combined with bevacizumab, 138, 139
epidemiology, 135
human epidermal growth factor receptor 2 antagonists, 155–156
immunotherapy, 154, 155
maintenance therapy
5-FU/leucovorin or capecitabine with or without bevacizumab, 144
bevacizumab and combinations, 145–148
chemotherapy-free interval, 145
definition, 144
EGFR inhibitors, 148
intermittent irinotecan, 146
leucovorin/5-FU therapy, 145
leucovorin/5-FU therapy without oxaliplatin, 145
optimal duration, 144
OPTIMOX1 study, 145
OPTIMOX2 study, 145
oxaliplatin, 144
stop-and-go strategies, 144
patient characteristics, 135
second-line therapy
chemotherapy, 148–149
EGFR and VEGF inhibitor combinations, 151
EGFR inhibitors, 149–150
ramucirumab, 151
VEGF inhibitors, 150
surgical options
adjuvant therapy after metastasectomy, 143
conversion therapy (neoadjuvant), 142, 143
hepatic metastasectomy, 142
liver-directed therapy, 143–144
pulmonary metastasectomy, 142
third-line therapy
chemotherapy, 152
EGFR-inhibitor studies, 152
palliative care, 151
regorafenib, 152–153
TAS-102, 153, 154
tumor-specific characteristics
BRAF mutation, 136
gene mutation testing, 137
microsatellite stability, 136
RAS mutations, 136
Metastatic disease, 66, 67
Metastatic lymph nodes, 276
Metastatic pancreas adenocarcinoma, 255
Metformin, 519, 520
Methotrexate (MTX), 635, 638, 663
Methylprednisolone, 676
Metoclopramide, 671, 673
mFOLFOX6, 640
Microbiota, 7
Micro ribonucleic acids, 484
Micro-RNAs (miRNA), 484, 580, 615
Microsatellite instability (MSI), 23, 43, 75, 115, 116, 317, 599, 602, 603
Microsatellite instability-high (MSI-H) tumors, 474, 602, 615
Microsatellites, 43
Microsatellite stability (MSS), 136, 599
tumors, 602, 603

Microscopic classification
architectural phenotype, 28
degree of differentiation, 28, 29
differentiation/histogenesis, 27
site of primary tumor, 27
Microsurgical epididymal sperm aspiration (MESA), 646
Microsurgical testicular sperm extraction (mTESE), 646
MicroTEC study (Microparticles and Thromboprophylaxis with Enoxaparin in Cancer), 375
Microwave ablation (MWA), 217, 554, 555
Microwave coagulation, 217
Midgut (distal small intestine and proximal colon) carcinoid tumors, 270
Midgut NETs, 271
Mid pelvis, 641
Milan criteria, 315
Minimal emetogenic chemotherapy, 673
Minimally invasive pancreaticoduodenectomy, 248
Minimally invasive surgery (MIS), 79, 80, 248
Mini nutritional assessment (MNA) test, 384
Minocycline, 680
Mismatch repair (MMR) deficiency, 5, 615, 617, 621, 622
Mismatch repair (MMR) genes, 16
Mitogen-activated protein kinase (MAPK) pathway, 190
MEK1/2, 481
Mitomycin, 672
Mitotic inhibitors, 635
Mitoxantrone, 638
Mixed adenoneuroendocrine carcinoma (MANEC), 74, 272
Mixed carcinoma, 74
Mixed hyperplastic/adenomatous polyps (MHPAPs), 39
MK2206, 88
ML17032 study, 83
Model of End-Stage Liver Disease (MELD) score, 212
Moderately differentiated hepatocellular carcinoma, 208, 209
Moderately emetogenic chemotherapy, 673
Modern cancer chemotherapy, 255
Modified Ann Arbor staging (Musshoff modification), 333, 338
Modified RECIST (mRECIST), 560
Modified TNM staging system, 333
Molecular alteration in oncogenesis of pancreatic ductal adenocarcinoma, 259
Molecular pathology, 16
tests, 21–23
Molecular profiling, 616
Monoclonal antibodies, 636, 637
Morphine, 679
MoTriColor program, 502
MPACT trial, 257
MR enterography, 457
mTOR pathway, 481, 625
Mucosal associated lymphoid tissue (MALT) lymphoma, 49
Mucositis, 673, 674
Multi-arm multi-stage (MAMS) trials, 503
Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, 496
Multicentric HCC, 215
Multidetector computed tomography (MDCT), 446
Multidimensional Fatigue Inventory (MFI-20), 676
Multi-disciplinary tumor board (MDT), 398, 399
Multinodular HCC, 215
Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) cohort, 369
Multiple lymphomatous polyposis, 340
Murine model of pancreatic cancer-induced thrombosis, 370
Murphy staging system, 315
Muscularis propria, 52
Musshoff modification/Lugano classification, 338
Mutations in DNA repair pathway genes, 260
MutL homolog 1 (hMLH1), 43
MutS homolog1 (hMSH2), 43
MutS homolog 6 (hMSH6) genes, 43
MutY-associated polyposis, 44
MUTYH-associated polyposis (MAP), 5
MUTYH gene, 596, 597
Myeloid derived suppressor cells (MDSCs), 521
MYH-associated polyposis (MAP), 596

N
NAPOLI-1 trial, 485
National Academy of Medicine, 363
National Cancer Database, 275
National Comprehensive Cancer Network (NCCN) GIST Task Force, 293
National Comprehensive Cancer Network (NCCN) guidelines, 235, 275, 352, 375, 415
National Institutes of Health (NIH) consensus for risk stratification for GIST, 293
National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial, 496
National Surgical Quality Improvement Program (NSQIP) database, 250
Natural killer T (NKT), 466
NK/T-cell markers, 337
Natural Orifice Transluminal Endoscopic Surgery Technique (NOTES), 533, 545, 546
Nausea and vomiting (N&V), 671
chemotherapy agent, 671
chemotherapy-induced nausea and vomiting
acute nausea and vomiting, 672
anticipatory nausea and vomiting, 672
breakthrough nausea and vomiting, 672, 673
chronic nausea and vomiting, 672, 673
delayed nausea and vomiting, 672
highly emetogenic chemotherapy, 673
low emetogenic chemotherapy, 673
minimal emetogenic chemotherapy, 673
moderately emetogenic chemotherapy, 673
non-pharmacological strategies, 673
refractory nausea and vomiting, 672, 673
etiology-based classification, 671
gastroparesis, 671
Neoadjuvant chemoradiotherapy, 640
Neoadjuvant chemotherapy (NAC), 170
Neoadjuvant endorectal brachytherapy, 436
Neoadjuvant radiation therapy, 434, 435, 640
Neo-adjuvant therapy, 424, 428, 435, 640
rectal cancer, 168
Neoangiogenesis, 217, 482
Neratinib, 619
Netherlands Cancer Registry, 269
NET liver metastases, 277
Netupitant, 673
Neuroendocrine tumors (NETs), 15, 46, 47, 74, 75, 97, 255, 321, 455
alfa-fetoprotein and human chorionic gonadotropin, 274
asymptomatic pancreatic, 276
baseline octreoscan, 274

bevacizumab, 280
bioactive products, 274
biochemical tests, 273, 274
cell lines and murine models of disease, 269
chemotherapy, 281
classification system, 269
colorectal pancreas, 272
cross-sectional imaging, 269
CT scan, 274
diagnosis and surveillance, 274
endocrine cells, 269
endoscopic procedures, 269, 273
evaluation and management, 275
functional positron emission tomography imaging, 275
gastrinoma (gastrin), 272
of gastrointestinal system, in children
  appendectomy, 320
  classification, 319
  clinical decision making, 319
  histology, 319
  incidence, 319
  laboratory markers, 319
  and pancreaticobiliary tracts, 269
  pancreaticoduodenectomy, 320
  proctoscopy, 321
  radiology, 319
  resection of involved segment and small bowel mesentery, 320
  sites, 319
  Surgery According to Extent of Disease, 320
  treatment, 320
  tumor markers, 320
glucagonoma (glucagon), 272
histological grade and differentiation, 271
hormonal secretion, 272
5-hydroxytryptophan, 274
incidence, 269
insulinoma (insulin), 272
magnetic resonance imaging, 274
mitotic counts/Ki-67 index, 272
molecular pathogenesis
  antitumor activity, TK inhibitor, 278
  anti-VEGF monoclonal antibody, 278
  cellular growth factors, 278
  everolimus, 279
  temsirolimus, 279
  VEGF-A, 279
with mTOR inhibitors, 279
multiphasic MRI, 274
nomenclature and classification, 272
non-neuroendocrine components, 272
octreoscan-SPECT accuracy, 275
pathologic assessment of tumor differentiation and grade, 275
platinum-based chemotherapy regimens, 275
prevalence, 269
primary treatment, 275
proliferative activity, 271
radiographic staging and tumor localization, 275
radiographic surveillance, 275
serotonin, 273
signs and symptoms, 273
small bowel/ampulla of vater, 272
somatostatinoma (somatostatin), 272, 278
somatostatin receptor scintigraphy, 274
stomach primary sites, 272
  surveillance strategy, 276
  systemic therapy, 275
  TNM staging of appendix, 272
  T-stage definition, 272
  tumor markers, 269
  tumor-node-metastasis-based system, 272
  in tumor registries, 269
  tyrosine kinase inhibitors, 280
  urinary 5-HIAA, 274
  vasoactive intestinal polypeptide, 272
  WHO classification, 272
Neurofibromatosis 1–associated GIST, 293, 321
Neuropathic pain, 679
Neuropsychiatric symptoms, 677, 678
  cancer-related neurological symptoms, 678
  cancer-related psychiatric symptoms, 678
  treatment-related neurological symptoms, 678
  treatment-related psychiatric symptoms, 678
Neurotrophic tropomyosin receptor kinase (NTRK) gene fusions, 621
Newcastle virus related vaccine (NDV), 468
Next-generation sequencing (NGS), 613, 626
  activated oncogenes, direct targeting of, 614
  DNA double-strand repair, 615, 616
  gene fusions, 614, 615
  matching treatments and molecular abnormalities
    diagnostic tool, 616, 617
    exploiting cancer cell vulnerabilities, synthetic lethality, 616
    genomic features in exceptional therapeutic responses, 617
    germline evaluation, 617
    mutant proteins, direct targeting of, 616
  mismatch repair, 615
  RNA, 614
  targeting molecular themes, 614
Nitrogen mustard, 638
Nivolumab, 154, 615, 617, 618, 623
Nivolumab monotherapy, 471, 493
N-nitroso compounds, 73
Nodular lymphoid hyperplasia, 336
Nonalcoholic fatty liver disease, 212
Nonalcoholic steatohepatitis (NASH), 516
Nonalcoholic steatohepatitis-related hepatocellular carcinoma, 212
Non-colorectal gastrointestinal cancers
  diet, 513
  obesity, control of, 516
  physical activity, 514, 515
Non-Hodgkin lymphomas (NHL), 315
Non-IPSID MALT lymphoma, 335, 338
Nonpancreatic periampullary adenocarcinomas, 240
Nonsteroidal anti-inflammatory drugs (NSAIDs), 8, 513, 518–520, 522–524
Non-surgical oncology, ESPEN guidelines, 386
Non-synonymous coding single-nucleotide variant in TP53, 316
North American Neuroendocrine Tumor Society (NANETS) guidelines, 278
Notch signaling pathway, 192, 261, 482
NSAIDs, *see* Nonsteroidal anti-inflammatory drugs (NSAIDs)
Nuclear export signals (NES), 485, 622
Nuclear expression of BCL-10 or NF-κ (kappa) B in gastric MALT, 331
Nuclear medicine, 658
Nucleo-cytoplasmic transport, 485
Nucleoporins (NUP214 and NUP88), 485
Nutritional awareness, 383
Nutritional management, 385
Nutritional problems, 670
Nutritional Risk Screening 2002 (NRS 2002) tool, 380

Nutritional support, 379
gastrointestinal cancer
ASPEN, 385
energy requirement, 385
ESPEN, 384, 385
food intake, 387
incurable and terminal patients, 390
oral intake, 387
perioperative malnutrition, 388
perioperative nutrition support, 389
perioperative period, 389
postoperative enteral nutrition, 389
postoperative feeding, 389
protein intake, 385
radiotherapy/chemotherapy, 387, 389
standard enteral formulae, 385
timing, 385
total energy expenditure, 385
tumor types, 385
therapy, 388
Nutrition Risk Screening 2002 (NRS-2002), 384
Nutrition support during adult anticancer treatment, 385

O
Obesity, 8
colorectal cancer
primary prevention, 515
secondary prevention, 515
tertiary prevention, 515, 516
non-colorectal gastrointestinal cancers, 516
Obstructive jaundice, 552
Octreotide, 671, 674, 675
Olanzapine, 673
Oligometastatic disease to liver, 433
Omics-based test, 498
Onartuzumab, 87
Oncogenic *KRAS* mutation, 258
OncoVax, 468
Oncovin, 638
Ondansetron, 671
Onsite adequacy evaluation, 18
Oocyte cryopreservation, 643, 644
Open coliseum HIPEC technique, 409
Open distal gastrectomy (ODG), 79
Open Hasson technique for laparoscopy, 403
Opioids, 675, 679
Oral nutritional supplements (ONS), 387, 670
Organogenesis, 655
Orthotopic liver transplantation (OLT), 186, 215
Orthotopic transplantation technique, 644
Osler Weber Rendu disease, 45
Ovarian cancer of epithelial origin (EOC), 416
Ovarian tissue cryopreservation, 644
Ovarian transposition, 645, 646
Overall survival (OS), 495, 496
OverStitchTM suturing device, 540
OX40, 473
Oxaliplatin, 125, 603, 635, 637, 638, 658, 672, 677–679
Oxaliplatin-based chemotherapy, 672
Oxaliplatin, Folinic Acid and 5-Fluorouracil (OFF), 257
Oxaliplatin-induced neurotoxicity, 356, 357

P
Paclitaxel, 658, 672
Pain, 678, 679
Palliative care, GI malignancies
brachytherapy, 351
communication during transitions, 363, 364
dysphagia, 351
high-dose brachytherapy, 351
incurable malignancies, 362
MBO, 352–354
natural history of disease, 362
palliative intent gastrectomy, 352
quality of life, 362
self-expanding metal stents, 351
shared decision-making, 363, 364
timing of, 362
Palliative care philosophy, 669
Palliative cytotoxic chemotherapy, 83, 84
Palliative gastrectomy, advanced gastric cancer, 352
Palmoplantar erythrodysesthesia (PPE), 680
Palonosetron, 673
Pancreatic adenocarcinoma, 255
adjuvant phase III trials, 242
tumor microenvironment, 260
Pancreatic cancer, 317, 428, 658
epidemiology, 4, 368
image-guided therapy and motion management, 431
IMRT, 428
innovative approaches, 255
irinotecan, 358
molecular analysis, clinical utility of
BRCA1/2 mutations/BRCAness, 622
KRAS mutations, 622
metabolic pathways, 622
mismatch-repair deficiency, 622
nuclear export factors, 622
molecular classification, 621, 622
particle therapy, 430, 431
patient selection, 255
positron emission tomography, 431
risk factors, 255
SBRT, 429, 430
screening
CT scan, 585
DNA microarray technology, 585
EUS, 585
evidence for, 585, 586
guidelines, 586
incidence of, 583
risk factors, 584, 585
sporadic, 255
surgical resection, 255
survival outcomes, 255
therapeutic approaches, 255
therapeutic prevention, 524
treatment strategies, 255
VMAT, 429
Pancreatic ductal adenocarcinoma (PDAC), 235, 255, 621
adjuvant and neoadjuvant therapies, 235
cetuximab, 480
clinical trial, 479, 482, 484
complete/R0 resection, 235
CT interpretation, 238
CT scan for staging, 238
diagnostic and surgical techniques, 235
diagnostic staging laparoscopy, 239
endoscopic ultrasound, 238, 239
imaging and screening modalities, 235, 239
KRAS and *CDK2NA*, 479
lapatinib, 480

magnetic resonance imaging, 238
nab-paclitaxel, 479
nimotuzumab, 480
ongoing trials, 486
patient care, 235
PET/CT, 239
positive trials, 485
positron emission tomography, 239
resectability rate, 235, 236
restaging, 239
signaling pathways, 479
single-agent therapy with oral fluoropyrimidine derivative S-1, 479
staging evaluation, 238
surgery, 479
surgical resection, 247
tissue diagnosis, 239
vascular involvement, 236
Pancreatic head adenocarcinoma, 249
Pancreatic intraepithelial neoplasia (PanIN), 585
Pancreatic malignant tumors, children, 316, 317
Pancreatic neuroendocrine tumors (PanNETs), 4, 624, 625
Pancreaticoduodenectomy, 244, 247, 248
at MDACC, 236
Pancreatoblastoma, 317
Pancreatoscopic-guided biopsies, 535
Panitumumab, 150, 189, 621, 635, 658, 672, 673, 680
Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study, 142
Papillary pattern, 28
Papillary/tubular carcinoma, 74
Papillomaviruses, 6
Paraneoplastic syndrome, 289, 677
Parenteral nutrition, 389
Paris staging system, 333, 338
for primary gastrointestinal tract lymphomas, 333
Partner abandonment, 643
Pathologic classifications, 24–27
Pathologic evaluation of tissue
ancillary methods, 21
benign, 16
cytopathologic evaluation, 16–18
immunohistochemical assessment, 21, 22
intra-procedural imprint/scrape cytology smears, 19
malignant, 16
molecular pathology tests, 21–23
resection margins, 19
specimen handling, 20, 21
surgical pathologic (histopathologic) evaluation, 19
Patient-generated subjective global assessment (PG-SGA), 380
Pediatric GIS cancers
in children
epithelial origin, 316–318
lymphoid origin, 315, 316
mesenchymal origin, 321, 322
neuroendocrine origin, 318–320
incidence, 311
postoperative staging system, 312
Pediatric GISTs, 321
Pegylated modified liposomes, 484
Pelvic peritonectomy, 406, 408
Pembrolizumab, 90, 471, 493, 501, 615, 618, 623, 624
Pencil beam scanning (PBS) proton therapy, 431
Peptide receptor radionuclide therapy (PRRT), 457
Peptide vaccines, 262, 467, 468
Percutaneous ablative therapies, 553
cryoablation, 554
hydrodissection and patient positioning, 553
irreversible electroporation, 554–556
microwave ablation, 554, 555
radiofrequency ablation, 553, 554
Percutaneous celiac plexus neurolysis, 354
Percutaneous endoscopic gastrostomy (PEG) placement, 388
Percutaneous ethanol injection (PEI), 216
Percutaneous gastrostomy placement (PGP), 566, 567
Percutaneous image-guided tissue sampling (PITS), 551, 552
Percutaneous nephrostomy (PCN), 553
Perforated appendiceal epithelial neoplasm, 413
Periampullary carcinoma, 249
Perineural invasion, 33
Perioperative nutrition support therapy, 389
Peripheral lymphadenopathies, 341
Peripheral neuropathy, 678
Peritoneal cancer index (PCI), 399
Peritoneal carcinomatosis (PC), 395, 413, 414, 452
diffuse type, 451
hematogenous spread, 451
imaging
computed tomography, 451, 453
MRI, 452, 453
PET-CT, 453, 454
intraperitoneal seeding, 451
peritoneal anatomy and physiology, 450, 451
Peritoneal cavity expander (PCE), 409
Peritoneal dissemination, 413, 414
Peritoneal malignancies
abdominal domain, 401
acute medical complications, 396
adverse effects and anesthetic effects on cardiac function, 401
anatomic structures, 399, 400
anesthesia, 401
anterior superior iliac spine, 399
ascites, 398
cardiac output, 402
central venous pressures, 402
chemotherapeutic agents, 402, 403
closed technique, 410
coagulopathy, 402
complete cytoreduction, 400
consensus guidelines, 416
CRS + HIPEC versus chemotherapy, 395
CT, 398
decision making process, 404
diagnosed comorbidities, 416
diagnostic laparoscopy, 403, 404
dopamine, 402
dynamic monitoring methods, 402
electrolyte disturbances, 402
endoscopy and laparoscopy, 398
fluid management, 402
hyperdynamic, vasodilatory state, 402
imaging modalities, 396, 417
intra-abdominal pressure, 403
intraoperative glycemic control, 403
intraoperative monitoring and patient safety, 401
intravascular volume, 402
laparoscopic staging, 403
long-term quality of life and recovery, 417
magnetic resonance imaging, 398, 417
minimal mucinous ascites and disease, 397
morbidity and mortality, 395
mucinous ascites, 398
multiplanar CT image reconstruction, 396
oncologic resection, 401
operative candidates, 399

Peritoneal malignancies (*cont.*)
patient positioning, 401
patient selection and diagnosis, 395
perioperative morbidity, 417
postoperative surveillance, 417
preoperative performance status, 396
primary lesions, 399
prognostic factor, 400
radical therapy, 401
safety and optimal cytoreduction, 401
sclerotic type, 396
scoring and stratifying systems, 401
surgical morbidity, 401
surgical resection, 396
synthetic colloid, 402
targeted resuscitation, 402
treatment pathways, 395
4-trochar approach to laparoscopic HIPEC, 403
urine output, 402
vascular resistance, 402
volume responsiveness, 402
Peritoneal mucinous carcinomatosis, 101, 102
Peritoneal surface disease severity score (PSDSS), 400, 401
Peritonectomy procedures, 405
Pernicious anemia, 576
and atrophic gastritis, 276
Peroral endoscopic myotomy (POEM), 540
Personal Health Questionnairre (PHQ-9), 359
Personalized therapy, 595
Pertuzumab, 618
PET-guided treatment algorithm, 63
Peutz-Jegher syndrome (PJS), 46, 584, 605, 606
Peyronie's disease, 273
PHACS (Prospective Randomized Multicenter Study of Dalteparin Prophylaxis in High-Risk Ambulatory Cancer Patients) trial, 375
Phosphatidylinositol 3-kinase (PI3K/Akt) pathway, 88, 190
Photodynamic therapy (PDT), 484, 541
Photosensitizers, 636
Physical activity, 8
colorectal cancer
primary prevention, 513, 514
secondary prevention, 514
tertiary prevention, 514
non-colorectal GI cancers, 514, 515
Physical therapy, 670
PI3K-AKT-mTOR inhibitors, 619
PI3K-AKT-mTOR pathway, 201
PI3K/akt pathway-induced stimulation of tissue factor transcription and translation, 370
PI3K inhibitor buparlisib, 259
Platelet phase and fibrin clot formation, 371
Platinum-induced neurotoxicity, GI, 356, 357
Play-the-winner designs, 501
13-valent pneumococcal conjugate vaccine (PCV13), 665
23-valent pneumococcal polysaccharide vaccine (PPSV23), 665
Pneumococcal vaccination, 664, 665
Poliovirus vaccination, 666, 667
Poly ADP ribose polymerase (PARP), 88, 89, 482
PARP1, 616
Polyamine inhibitors, 520, 521
Polymerase chain reaction (PCR) testing, 43, 332
of IgH gene rearrangements, 331
Polymorphism in uridine diphosphate glucuronosyltransferase (UGT) 1A1 gene, 263
Polyp burden, 597
Polypoid colitis-associated dysplasia, 42
Polypoid lesions, 19
Polyposis syndrome
with colorectal carcinoma, 317
colorectal MALT lymphoma, 340
juvenile polyposis, 606, 607
Peutz-Jegher syndrome, 605, 606
Polyp Prevention Trial, 512
Poorly differentiated hepatocellular carcinoma, 50, 209
Poorly differentiated neuroendocrine carcinomas, 271
Portal hypertension, 212
Portal vein embolization (PVE), 556–558
Positron emission tomography-computed tomography (PET-CT)
colorectal cancers, 458
esophageal cancer, 447
gastric adenocarcinoma, 450
peritoneal carcinomatosis, 453, 454
small bowel, malignant disease of, 457
Positron emission tomography-directed therapy, esophageal cancer, 425
Positron emission tomography (PET), pancreatic cancer, 431
Positron emission tomography Response Criteria in Solid Tumors (PERCIST) 1.0, 497
Post-embolization syndrome (PES), 561, 563
Post-hepatic jaundice, 675
Postmeiotic segregation increased 2 (hPMS2), 43
Postneoadjuvant therapy (ypTNM), 57
Postoperative octreotide therapy, 276
POSTTEXT, 314
Post-transplant immunosuppression, 330
Post-transplant lymphoproliferative disorders, 330
Predicted and peritoneal surface disease severity score (PSDSS), 399
Pregnancy
gastrointestinal cancers
breastfeeding, 659
chemotherapy agents, 658
diagnosis and staging imaging, 656, 657
incidence of, 655
management, 655
nuclear medicine, 658
placental metastasis, 659, 660
radiation therapy, 659
radiological diagnosis, 657, 658
stages and fetal development, 655, 656
surgery, 659
systemic therapy, 658, 659
treatment modulaties, 658
tests, 332
Prehepatic jaundice, 675
Premalignant squamous cell neoplastic lesions, 176–177
Preoperative biliary drainage, 543
Preoperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma Trial (POET), 424
PRETEXT (pretreatment extent of disease), 314
classification system, 313
stage I and II, 313
Pre-vivors, 604
Primary cholangiocarcinoma/metastatic adenocarcinoma, 211
Primary colonic T-cell lymphoma, 50
Primary effusion lymphoma (PEL), 50
Primary gastric adenocarcinoma (GAC), in children, 316
Primary intestinal follicular lymphoma, 338
Primary intestinal non-Hodgkin's lymphomas, 315
Primary liver cancer, 3
Primary lymphomas, 455
Primary mediastinal DLBCL, 332
Primary non-Hodgkin lymphomas of GI tract, 329

Primitive neuroectodermal tumor (PNET) of pancreas, 317
Prior surgery score (PSS), 399
Probiotics, 674
Procarbazine, 638
Prognostic awareness, GI malignancies, 359–361
Programmed cell death protein 1 (PD-1), 21, 90, 192, 471
Programmed death ligand 1 (PD-L1), 21, 90, 192
  on tumor cell's surface, 262
Progression-free survival (PFS), 496
Prophylactic cholecystectomy, 276
Prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer, 414
Prophylaxis of Thromboembolism During Chemotherapy (PROTECHT) trial, 373
Prostaglandin-endoperoxide synthase 2 (PTGS2)-positive tumors, 514
Prothrombotic pathways in cancer, 369
Proton/photon therapy, 432
Proton pump inhibitor (PPI) therapy, 522
  NETs, 274, 275
Proton therapy, 423, 425, 428, 430, 432–434
  HCC, 220, 432
  in rectal cancer, 435
Pruritus, 676
P-selectin, 371
Pseudoinvasion, 39
Pseudomyxoma peritonei (PMP), 101, 102
Psychostimulants, 676
Pulmonary embolism (PE), 367
Pulmonary metastasectomy, 142
Pylorus-preserving gastrectomy (PPG), 81
Pylorus-preserving PD (PPPD), 248

Q

QLQ-CIPN20 tool, 357
Quality of life (QOL), 428, 669, 676
Quick And Simple And Reliable (QUASAR) phase III trial, 114

R

RADIANT 2 trial, 279
RADIANT-3 trial, 279
Radiation-induced liver disease in patients with HCC, 220
Radiation technology, 355
Radiation therapy (RT), 663–665
  anal cancer, 436, 437
    charged particle therapy, 438
    IMRT, 437, 438
  cholangiocarcinoma
    particle therapy, 434
    SBRT, 433
    unresectable intrahepatic cholangiocarcinoma, 433
  esophageal cancer (*see* Esophageal cancer, RT)
  fertility preservation, 639, 640
    CAPOX, 640
    females, 640, 641
    males, 641, 642
    mFOLFOX6, 640
    neoadjuvant radiotherapy, 640
    Swedish trial, 639
    total mesorectal excision, 639
  gallbladder cancer, 434
  gastric cancer
    charged particle therapy, 428
    IMRT, 427, 428
    Intergroup/SWOG trial, 427
    MAGIC trial, 427
  heavy particle therapy, 423
  hepatocellular carcinoma
    charged particle therapy, 432, 433
    SBRT, 431, 432
  induced enteritis, 318
  intensity-modulated radiation therapy, 421, 422
  intraoperative radiation therapy, 423
  liver cancer, 219
  oligometastatic disease to liver, 433
  pancreatic cancer, 428
    image-guided therapy and motion management, 431
    IMRT, 428
    particle therapy, 430, 431
    positron emission tomography, 431
    SBRT, 429, 430
    VMAT, 429
  pregnancy, gastrointestinal cancers, 659
  rectal cancer, 434, 435, 641
    charged particle therapy, 435, 436
    endorectal brachytherapy, 436
    IMRT, 435
  skin problems, 680
  stereotactic body radiation therapy, 423
  volumetric modulated arc therapy, 422
Radiation Therapy Oncology Group (RTOG) trials, 240, 247, 425
Radioembolization, 561, 562
  with Yttrium-90, HCC, 216, 218
Radio-frequency ablation (RFA), 59, 216, 217, 522, 538, 540, 541, 553, 554, 575
  adverse events, 541
  applications for, 541
  EUS-guided pancreatic indications for, 541
  high-grade dysplasia, 540
  low-grade dysplasia, 540
  squamous dysplasia and early SCCs, 541
Radiologic imaging
  colon cancers, 461
    computed tomography colonography, 461
    MRC, 461, 462
  tests, HCC, 583
RAF/MEK/ERK signaling cascade, 481
RAINBOW trial, 86
Ramucirumab, 85, 151, 619, 672
Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer-2 (REAL-2) trial, 83, 371
Ranitidine, 671
Rapid on-site cytology evaluation (ROSE), 534
RAS-RAF-MEK-MAPK pathway, 201
Recombivax HB®, 666
Rectal ampulla, 51
Rectal cancer (RC), 422, 434, 435, 458–460
  adjuvant chemotherapy
    5-FU-based therapy, 123–125
    oxaliplatin, 125
  charged particle therapy, 435, 436
  chemoradiation
    NCCTG 794751 study, 118
    neoadjuvant versus adjuvant chemoradiation, 118, 119
    NSABP R-01 randomized trial, 118
  choice of systemic therapy
    adjuvant and neo-adjuvant therapy, 168
    anti-EGFR monoclonal antibody, 167
    bevacizumab, 168
    capecitabine, 166, 167

Rectal cancer (RC) (*cont.*)
cetuximab, 167
EGFR inhibitors, 167
fluoropyrimidine, 167
5-fluorouracil, 166
gefitinib, 167
irinotecan, 166, 167
oxaliplatin, 166, 167
panitumumab, 167, 168
VEGF monoclonal antibody, 168
circumferential resection margin, 117, 118
clinical stage T0N0 after neoadjuvant therapy, 168, 169
diagnosis, 117
endorectal brachytherapy, 436
imaging, MRI, 458, 461
IMRT, 435
neoadjuvant chemoradiation
bevacizumab, 121
cetuximab, 121
chemotherapy, 124–126
with fluoropyrimidines, 119, 120
irinotecan, 121
oxaliplatin, 121, 122
panitumumab, 121
short course versus long course radiation, 121–123
NOTES approach, 162
optimal delivery, 165–166
optimal pre-therapy staging, 117
optimal surgical approach, 165–166
planning therapy, 117
preoperative radiotherapy, 162–163
preoperative versus postoperative CRT, 163–165
robotic platform, 162
staging, 117, 161, 162
total neoadjuvant therapy, 170
watch and wait strategy, 168
Rectal neuroendocrine tumor, 271, 320
Recurrent tumors, 29
Recycling, 136
Reduction surgery, 80, 81
Refeeding syndrome, 388
Refractory nausea and vomiting, 672, 673
REGARD trial, 85
Regional pancreatectomy, 249
Regorafenib, 86, 152, 153, 623, 672, 674
Regulatory T cells (Tregs), 466, 467, 471
Relative risks (RRs), 4
Renal perfusion, vasopressors, 402
Resectable metastatic colorectal cancer
combination therapy, 127
neoadjuvant treatment, 127
resected pulmonary metastases, 127, 128
systemic therapy, 126
Resectable PDAC
adjuvant chemoradiation, 240
with 5-FU, 239
adjuvant gemcitabine, 240
adjuvant systemic chemotherapy, 241
arterial encasement, 235
CONKO-001 calling for single-agent gemcitabine, 241
conventional chemotherapeutic and/or chemoradiation regimens, 241
cytotoxic therapies, 241
definition, 235, 237
erlotinib, 241
5-FU/gemcitabine chemotherapy, 240
gemcitabine, 241
local, regional/systemic recurrence, 239
multimodal therapeutic strategies, 239
neoadjuvant and adjuvant chemoradiation, 239
adjuvant therapy, 243
benefits, 242
biliary tree decompression, 242
chemoradiation protocols, 242, 244
chemotherapy administration, 242
combination gemcitabine-cisplatin, 244
complications, 242
external beam intraoperative radiation therapy, 243
gemcitabine, 243
gemcitabine plus cisplatin, 244
in high-risk resectable disease, 245
locoregional disease control, 243
locoregional recurrence, 242
mitomycin, 243
multimodal therapy, 242
neoadjuvant 5-FU-based chemoradiation, 243
pancreaticoduodenectomy, 243
pancreaticojejunal anastomotic leak rate, 242
phase II multi-institutional neoadjuvant trial, 242, 244
safety and feasibility, 243
side-effect profiles, 243, 245
surgical resection, 242
trials, 244
tumor sampling, 242
radiation therapy, 239
randomized controlled adjuvant trials, 241
R0/R1 resection, 240, 241
venous occlusion, 235
Resection margins, 31
Residual tumor, 29
Respiratory gating, 220
Response evaluation criteria in solid tumor (RECIST) criteria, 246, 277, 428, 497, 560
Retinoids, 680
Robot-assisted surgery, 81
Rofecoxib, 577
ROMANA III trial, 383
ROS1 fusions, 191, 192
Rotterdam Symptom Checklist (RSCL), 676

S
S-adenosylmethionine (SAMe), 524
SAKK 41/06 trial, 146
Sapaniserib, 625
Sarcomatoid carcinoma, 209
Sarcopenia, 384
Satellite lesions (skip lesions), 33
SAVE-ONCO trial, 373
SBRT, *see* Stereotactic body radiation therapy (SBRT)
Scandinavian Sarcoma Group study, SSGXVIII, 297
Scirrhous carcinoma, 209
Screening, 573
colorectal cancer
average risk populations, 577, 581
carcinoembryonic antigen assay, 580
colonoscopy, 578–580
computed tomography colonography, 579
double-contrast barium enema, 579
fecal occult blood testing, 579, 580
flexible sigmoidoscopy, 579
high risk genetic syndromes, 578

high risk populations, 577, 578, 581
incidence of, 577
microRNAs, 580
modalities, 578
risk factors, 577
stool-based DNA testing, 580
definition, 573
esophageal cancer
esophageal adenocarcinoma, 574
esophageal capsule endoscopy, 574
esophago-gastro-duodenoscopy, 574
recommendations and guidelines, 575
risk factors, 574
squamous cell carcinoma, 574
gastric cancer
esophago-gastro-duodenoscopy, 576
incidence of, 575
population-based screening, 576
recommendations and guidelines, 577
risk factors, 575, 576
serological testing, 576, 577
X-ray photofluorography, 576
incidence and death rates, United States, 573
liver cancer (*see* Hepatocellular carcinoma (HCC))
pancreatic cancer
CT scan, 585
DNA microarray technology, 585
EUS, 585
evidence for, 585, 586
guidelines, 586
incidence of, 583
risk factors, 584, 585
Secreted protein acidic and rich in cysteine (SPARC), 263
Selective internal radiotherapy (SIRT), 561
with Y-90, 561–563
Selinexor, 485
Semiquantitative approach, 28
SEMS, *see* Stents or self-expandable metal stents (SEMSs)
Sequence by synthesis (SBS), 614
Sequential compression devices (SCD), 401
Serological testing, 576, 577, 582
Serotonin testing, NETs, 274
Serrated polyposis syndrome, 39, 44
Serum pepsinogen testing, 577
Sessile serrated adenoma (SSA), 39–41
with cytological dysplasia, 39
Sessile serrated polyps (SSP), 40
Severe combined immune deficiency (SCID), 667
Sex hormone-related hepatocellular carcinoma, 212
Short tandem repeats (STRs), 43
Siewert type I tumor, 56
Siewert type II tumor, 56
Siewert type III tumor, 56
Sigmoidoscopy, 579
Signal transducer and activator (*STAT*) pathway, 260
Signet ring adenocarcinoma, 609
Signet ring features, 43
Simplified PCI, 399
Simultaneous integrated boost (SIB), 426, 432
Single-antigen vaccines, 666
Single-incision needle knife (SINK) biopsy, 535
Single nucleotide polymorphism (SNP) array, 76
SIOPEL PRETEXT staging system, 312
SIOPEL, risk stratification, 313
SIR-Spheres, 561
Skeletal muscle atrophy, 381
Skin problems, 679
with cytotoxic agents, 680
radiation therapies, 680
with targeted therapies, 680
16S ribosomal RNA hypervariable region, 7
Small, asymptomatic, well-differentiated pancreatic NETs, 275
Small bowel adenocarcinoma (SBA)
advanced stage disease, 98
clinical presentation, 97
clinical staging, 97, 98
diagnosis, 97
epidemiology, 97
localized early stage disease, 98
molecular classification, 619
prognostic factors, 97
Small bowel malignancies, 97, 407
adenocarcinoma, 454
imaging, 454
computed tomography, 454–456
MRI, 456, 457
PET-CT, 457
somatostatin receptor-based, 457
incidence of, 454
types, 408
Small bowel NETs, 271, 276
Small colonic biopsies, 37
Small intestinal lymphomas, primary
antibiotics, 338
B-cell origin, 336
B-cell/T-cell, 335
blood count and peripheral blood smear, 335
Campylobacter infection, 336
characteristic imaging, 336
chemotherapy, 338
chronic inflammation, 336
clinical trials, 339
cross-sectional imaging, 337
CT scans of chest and abdomen, 336
diagnosis, 336, 337
distribution of, 335
duodenum, 335
EATL, 335
endoscopic findings and tumor location, 337
etiological factors, 335
extranodal NK/T-cell lymphomas, 335, 339
follow-up, 339
gluten-free diet, 339
H. pylori, 336
in ileum, 335
immunosuppressive agents, 336
incidence, 336
intestinal involvement, 335
jejunum, 335
laboratory studies and bone marrow biopsy, 337
laparotomy, 338
MALT lymphomas, 335
nutritional support, 339
pathological confirmation, 337
prognosis, 338
radiation therapy to abdomen, 336, 338
R-CHOP, 339
recurrence, 339
resection, 338
risk factors, 336
risk of perforation, 335

Small intestinal lymphomas, primary (*cont.*)
staging, 338
tools, 337
submucosal lymphoid tissue, 335
surgical intervention, 338
surveillance, 339
T-cell lymphomas, 335
tetracycline to anthracycline-based chemotherapeutic regimens, 338
tissue sampling, 337
treatment, 338, 339
Small intestinal obstruction, 544, 545
Small intestine
histological types, 2
incidence, 2
mortality, 2
Small intestine NETs (SI-NETs), 624
Small-molecule inhibitor of multiple signaling pathways, 481
Small-molecule nuclear export inhibitors, 485
Small nodular and polypoid tumors, 340
Small non-invasive resectable nodules in small bowel mesentery, 408
Small surgical pathology specimens, 21
Solid pseudopapillary tumor of the pancreas, 316
Solid/trabecular pattern, 28
Somatostatin analogs, 277, 278
therapy, 674
Somatostatin receptor-based imaging techniques, 457
Somatostatin receptor scintigraphy (octreoscan), 274, 275, 277
Sorafenib, 432, 561, 623, 658, 680
antitumor effect, 280
Southern Europe New Drugs Organization (SENDO) foundation data, 373
Southwest Oncology Group (SWOG), 247, 258
Spermatogenesis, 635, 639, 641
Sperm cryopreservation, 646, 647
Spindle poisons mitotic inhibitor, 636
Sporadic GIST (nonfamilial/nonhereditary), 293
Sporadic juvenile polyps, 45
Squamous cell cancer (SCC), 316, 445, 574, 617
clinical (cTNM), 57
distant metastasis (M), 57
histologic grade (G), 57
location, 57
occurence, 1
pathological (pTNM), 57
postneoadjuvant therapy (ypTNM), 57
primary tumor (T), 57
regional lymph nodes (N), 57
risk factors, 1, 574
screening
EGD, 574
recommendations and guidelines, 574, 575
Squamous cell carcinoma of the anal canal (SCCA)
biomarkers, 182
cancer types, 176
clinical and pathologic staging, 178
delayed anatomical complication, 181
diagnosis, 178
epidemiology, 175
hematological complications, 181
long-term radiation treatment, 181
premalignant squamous cell neoplastic lesions, 176–177
prevention, 182
prognostic factors, 182
risk factors
human immunodeficiency virus, 175
human papilloma virus, 175
pelvic radiation therapy, 176
sexual orientation, 175
smoking, 175
screening, 177
short-term complications, 181
surveillance, 181
treatment
HIV+ patients, 181
locally advanced, 179, 180
locally persistent, progressive or recurrent, 181
metastatic disease, 180
regional, 179
SSA, *see* Sessile serrated adenoma (SSA)
Staging classifications / designator rules, 31–32
Standard RECIST (Response Evaluation Criteria in Solid Tumors), 300
Stellate mesentery, 451
Stem and progenitor cells, 261
Stem cell factor inhibitor BBI608, 261
Stem cells, 261
Stents/self-expandable metal stents (SEMSs), 541–543, 545, 563
Stereotactic ablative body radiation (SABR), 423
Stereotactic body radiation therapy (SBRT), 219, 246, 421, 423, 543
in cholangiocarcinoma, 433, 434
in hepatocellular carcinoma, 431, 432
oligometastatic disease to the liver, 432, 433
in pancreatic cancer, 429, 430
Stomach cancer, *see* Gastric cancer
Stomatitis, 673
Stool-based DNA testing, 580
Subdiaphragmatic peritonectomy, 405
Subjective global assessment (SGA), 384
Submucosal injections, 536, 537
Sucralfate enemas, 674
Sulfasalazine, 674
Sulindac, 520, 521, 596
Sunitinib, 672
Superficial migratory thrombophlebitis, 677
Superior hypogastric plexus block (SHPB), 679
Surgical pathologic (histopathologic) evaluation, 16, 19
Surveillance, Epidemiology and End Results (SEER) database, 269, 368
Syndromic polyps, 45
Symptom management for GI cancers
diarrhea, 673
fatigue, 669, 676
hematological complications, 677
jaundice, 675, 676
malignant ascites, 675
malignant bowel obstruction, 674, 675
mucositis, 673, 674
nausea and vomiting (*see* Nausea and vomiting (N&V))
neuropsychiatric symptoms
cancer-related neurological symptoms, 678
cancer-related psychiatric symptoms, 678
treatment-related neurological symptoms, 678
treatment-related psychiatric symptoms, 678
nutritional problems, 670
pain, 678, 679
skin problems, 679
with cytotoxic agents, 680
radiation therapies, 680
with targeted therapies, 680
Systemic chemotherapy, 659

T
Tamoxifen, 596
Tarextuman, 261
Targeting downstream signaling pathways
  MAPK pathway, 190
  PI3k/Akt pathway, 190
Taxane, 637, 659, 678
T-cell histiocyte rich large B-cell lymphoma, 332
T-cell immunoglobulin and mucin containing protein-3 (TIM-3), 472
T-cell lymphomas, 50, 337
Technetium 99m-labeled macroaggregated albumin (MAA), 562
Tegafur Uracil, 672
Telotristat-ethyl, 674
Testicular sperm aspiration (TESA), 646
Testicular sperm extraction (TESE), 646
Testicular tissue cryopreservation, 646
Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination, 666
TH-302, 485
The Cancer Genome Atlas (TCGA) project, 613
Thermogenesis, 381
Thioguanine (6-TG), 638
Thiotepa, 638
3-arm AIO-0207 trial, 147
Three-dimensional conformal radiation therapy (3D-CRT), 421, 424, 427–429, 431, 433, 435, 437, 438, 641
Three Regimens of Eloxatin Evaluation (TREE) trial, 138
Thrombocytopenia, 677
Thromboembolism, 367, 677
Thrombogenesis under physiologic conditions, 370
Thromboprophylaxis in cancers
  anticoagulants, 375
  enoxaparin prophylaxis, 375
  prevalence and incidence, 373
  risk reduction, 375
  sP-selectin levels, 375
Time to failure (TTF), 147
Tissue acquisition
  cholangioscopic- and pancreatoscopic-guided biopsies, 535
  endoscopic ultrasound–fine needle aspiration, 533, 534
  endoscopic ultrasound–fine needle biopsy, 534, 535
  gastrointestinal subepithelial lesions, biopsy of, 535
  optical biopsy, 533
TNM staging, 15–16, 29–33
Tobacco-induced carcinogenesis, 4
Tobacco smoke, 4
Topical clindamycine, 680
Topical tazarotene, 680
Topoisomerase inhibitors, 636
Toremifene, 596
Total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO), 605
Total neoadjuvant therapy (TNT), 170
Total/partial anterior parietal peritonectomy, 405
Traditional serrated adenomas (TSA), 39, 41
Traditional vs. PPPD, 248
Transanal minilaparoscopy-assisted natural orifice transluminal endoscopic surgery approach, 162
Transarterial chemoembolization (TACE), 558–560
  cisplatin, 558
  complications, 560
  doxorubicin, 558
  HCC, 558, 559
  mCRC, 558
  outcomes, 561
  DEB-TACE, 561
  HepaSphere, 561
  post-embolization syndrome, 561
  polymer-based drug-eluting microspheres, 558
  pre-treatment imaging, 560
  response assessment after, 560
Transarterial radioembolization (TARE), 143, 144
  HCC, 216
Transient elastography, 582
Transitional liver cell tumor, 314
Trastuzumab, 618, 621, 672
Trastuzumab emtansine, 85
Tregs, *see* Regulatory T cells (Tregs)
Tremelimumab, 89, 471, 473
Trifluridine/tipiracil (TAS-102), 153, 154
Triple endoscopy, 575
Trousseau syndrome in mouse models, 371
Tubular/tubullovillous adenomas, 39, 40
Tumoral EGFR expressio, 258
Tumoral hypoxia, 259, 260
Tumor associated antigen (TAA), 521
Tumor associated macrophages (TAM) infiltration, 89
Tumor budding, 28
Tumor cell entrapment hypothesis, 405
Tumor cell heterogeneity, 626
Tumor cell-induced platelet aggregation (TCIPA), 371
Tumor deposits (TD), 33
Tumor infiltrating lymphocytes, 598
Tumor infiltrating macrophages (TIM), 466
Tumor necrosis and left liver hypertrophy, 213
Tumor periphery, 33
Tumor stroma, 483
Tumor-suppressor *BRCA2* gene, 258, 482
Tumor testing, 602
Typical tubular adenoma, 41
Tyrosine kinase inhibitors (TKIs), 258, 480, 636, 637
  of epidermal growth factor receptor, 258
  NETs, 280

U
UGT1A1 polymorphisms, 358
Ulcerative colitis (UC), 577
Ulcerative enteritis, 336
Umbrella trials, 502
Unresectable disease, 65, 66
Unresectable extrahepatic cholangiocarcinoma, 433
Unresectable intrahepatic cholangiocarcinoma, 433, 434
Unresectable tumors of rectum and anus, 318
Upper gastrointestinal series (UGIS), 577
Upper gastrointestinal tract surveillance, 605
Upper GI series (UGIS), *see* X-ray photofluorography
Upper pelvis, 641
Urea breath testing, 334
Urelumab, 473
Urinary 5-HIAA testing, carcinoid syndrome, 274
Urinary obstruction, 552, 553

V
Vaccination
  in adults with solid cancer, 664
    Haemophilus influenzae type b (Hib), 665
    hepatitis A, 666
    hepatitis B, 666

household contacts of immunocompromised patients, 667
human papillomavirus vaccine, 666
influenza, 664
meningococcal vaccine, 666
MMR, 665
pneumococcal, 664, 665
poliovirus vaccination, 666, 667
tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, 666
varicella, 665
zoster, 665
immunosuppression, degree of, 663
peptide vaccines, 467, 468
safety in immunocompromised individuals, 663
timing of immunization, 664
whole tumor vaccines, 467
Vaccine-preventable diseases, 663
13-valent pneumococcal conjugate vaccine (PCV13), 665
23-valent pneumococcal polysaccharide vaccine (PPSV23), 665
VALUE strategy, 362
Varian real-time position management system, 219
Varicella vaccination, 665
Vascular endothelial growth factor (VEGF) pathway, 200, 201, 217, 466, 637, 675
bevacizumab, 188
cerdiranib, 188
neoangiogenesis, 482
sorafenib, 188
sunitinib, 188
vandetanib, 188, 189
Vascular endothelial growth factor receptor blockade, 619
Vascular endothelial growth factors, NETs, 279, 280
Vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathway, 85, 259
Vascular epidermal growth factor (VEGF), 673–674
Vascular invasion, 215
Vascular resection and reconstruction, pancreaticoduodenectomy, 249, 250
Vector-based vaccines, 262
Velban, 638
Vemurafenib, 620
Venous invasion by tumor, 33
Venous thromboembolism (VTE) in cancer, 367
treatment
anticoagulation, 376
ASCO guidelines, 376
dalteparin, 376
and prophylaxis, 374
risk tools and predictive biomarkers, 376
survival and outcomes, 376
warfarin, 376
Vienna Cancer and Thrombosis Study (CATS), 372
Villous adenomas, 40
Vinblastine, 638
Vincristine, 638
Viral vectors, 262
Virchow's triad, 370
Visceral obesity, 8
Vitamin D, 519
Vitamin K antagonist, 677
Vitrification of mature oocytes, 645
Volumetric modulated arc therapy (VMAT), 422, 438, 641
gastric cancer, 427, 428
in pancreatic cancer, 429
V325 phase III study, 83

W
Weight loss, 383
Well-differentiated neuroendocrine tumor, 46, 47
Well-intermediate-grade pancreatic gastrointestinal neuroendocrine tumors and carcinomas, 211
Whipple resection (pancreaticoduodenectomy), 99, 100
WHO grading system, 47
Whole-cell vaccines, 261, 262
Whole-genome shotgun, 7
Whole tumor vaccines, 467
Wild-type GIST (no mutation), 322
Wnt-β(beta)-catenin pathway, 482
Wnt signaling, 620
World Health Organization (WHO), 271
classification system, 335
IARC Monographs program, 7
Wotherspoon histological index, 334

X
XELOX (capecitabine, oxaliplatin), 637, 638
Xiphoidectomy, 405
X-ray photofluorography, 576

Z
Ziv-aflibercept, 150, 151, 672
Zollinger-Ellison syndrome, 276
Zoster vaccination, 665