Comprehensive Rectal Cancer Care

Mary Kwaan
Andrew Zbar
Editors

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Editors
Mary Kwaan
University of California, Los Angeles
Los Angeles, CA
USA

Andrew Zbar
University of Melbourne
Victoria, VIC
Australia

University of Tel Aviv Israel
Tel Aviv
Israel

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This book is dedicated to the memory of Professor Lars Påhlman (1946–2015): visionary, mentor and friend.

My work on this book is inspired by the enthusiasm of Dr. Stanley M. Goldberg, an unparalleled and tireless advocate for the advancement of colorectal surgery and of colorectal surgeons.

— Mary Kwaan

This book is dedicated to my parents and to those in our profession who with integrity are without prejudice.

— Andrew Zbar

Foreword

Of all major malignancies at this time, rectal cancer is perhaps the one most dramatically involved in the collision between centrally directed guidelines and individual patient choices that often seem preferable to the so-called standard of care. Prospective randomised controlled trials (PRCTs), guidelines, and indeed the whole concept of level 1 evidence itself are failing to keep abreast of burgeoning technologies and new developments. The treatment choices mostly precede operative treatment and therefore demand immediate decisions about widely differing specialties – induction chemotherapy?, neo-adjuvant chemo-radiotherapy?, re-appraisal – watch and wait or major life-altering surgery?, TME or local excision?, colostomy or ultra-low resection and anastomosis? open, keyhole, robotic, or trans-anal? … all decisions which must be made before the invasive moment!

The surgeon remains the lion in this complex jungle, but details of how to optimise his performance remain often incomplete; for example, whether the all-important autonomic nerve plexuses and neurovascular bundles may be best preserved by dissection from above or from below has yet to be determined. For the first time in the history of our specialty, within the surgery world alone, there are no surgeons optimally skilled in all the alternative methods – which makes a valid PRCT literally impossible, since to compare two techniques scientifically the personal skill element should be excluded. Add to these immediate decisions the rapid advances in imaging, genetic sequencing, checkpoint inhibition immunotherapies, the microbiome …….. and you have a single malignancy in which no single specialist doctor can any longer be completely informed.

How then can the responsible specialist advise a patient adequately in a world where the 4 Cs – **C**ommunication, **C**ourtesy, and **C**ontinuity of **C**are seem sometimes to be disappearing. Slavish adherence to guidelines may be unacceptable to the well-informed cancer patient faced with dramatic new alternatives; these now include the avoidance of over treatment for early lesions and for even advanced lesions the avoidance of surgery and colostomy altogether – indeed all the perceived terrors that have so long attended this dread diagnosis are close to yielding in certain

cases to completely informed modern planning. The patient should never have to look back with regret and question whether the treatment he received was truly optimal. This book will go a long way towards preparing us to meet this challenge.

Professor R. J. Heald, CBE, MChir, FRCS
Chairman of Colorectal Cancer Program
Champalimaud Institute, Lisbon, Portugal

Trustee Pelican Centre, Basingstoke, UK

Current Chair European Academy of
Robotic Colorectal Surgeons
Lisbon, Portugal

Preface

The management landscape of rectal cancer is changing at such a rate that one hesitates to put out a book with the title 'Comprehensive Rectal Cancer Care'. The aim in this volume is to express a snapshot in time of the current status of the decision making surrounding tailored rectal cancer management which is driven by the latest evidence base. Although surgery remains the mainstay of treatment, it too is part of a dynamic world that now must incorporate the rise of minimally invasive approaches, technical advances in robotics and the selective use of transanal technology. Add to this the option of organ preservation. Improvements in the management and in outcome analysis have come from all sides with optimization in surgical techniques, standardization and quality control of pathology assessments and with multidisciplinary team management.

This book is divided into 11 sections. It begins with epidemiology, current approaches to imaging and the pathological assessment of rectal cancer and tumor regression following preoperative therapies. The modern surgical alternatives available are considered next, outlining the embryological aspects which define total mesorectal excision (TME) along with a description of the transformative impact of TME on outcomes. There is then reference to the indications, contraindications and techniques of local excision, transanal TME (taTME), intersphincteric excision, modern abdominoperineal resection, multivisceral resection, lateral pelvic lymphadenectomy and the construction of neorectal reservoirs.

In this morass of data, we will need in the future to interpret the results of the newer non-inferiority technical trials, the current data of which are somewhat mixed showing general oncologic equivalency between minimally invasive and open surgery but also reporting some concerning results from some National trials regarding the completeness of laparoscopic rectal resections. The introduction of the robot appears to obviate some of the technical difficulties imposed within the pelvis by laparoscopy even though its use may be more time consuming and more expensive. The wider expansion of transanal total mesorectal excision (TaTME) requires specialized training and imposes particular technical challenges necessitating access to cadaveric courses and ongoing mentoring as recently suggested by an international group recommending a structured training curriculum.

The next section of this book presents the Continental and American approaches towards radiotherapy (RT) and the chronological development of adjuvant and preoperative RT which began in Sweden where the beneficial impact on local recurrence was first proven. The gamut of chemotherapies and the newer immunotherapeutic trials are considered as part of an ever changing field. We have deliberately attempted to incorporate European, North American and Australasian perspectives towards the difficult management of locoregionally recurrent rectal cancer and for the treatment of Stage IV disease (either with or without the primary tumor *in situ*). There is also a brief consideration of the rarer specialist rectal tumors. As all forms of rectal cancer therapy (including organ preservation) are associated with a significant impact on the functioning of our patients, instruments assessing their quality of life are discussed along with caveats concerning the interpretation of economic data as it pertains to that part of the health care expenditure which is earmarked for the totality of rectal cancer care.

The studies to watch out for in the future are going to be those which extend the new chemotherapies and biologicals in intensified protocols designed to enhance the response of the primary and to reduce the risk of distant metastasis. The application of more intensive treatment is awaited too in the elderly where conventional postoperative adjuvant therapy may presently be indicated but where its administration is anticipated to be either dose restricted or interrupted. One study to keep an eye on is the STAR-TRec trial, a recently initiated multi-centered, 3-arm feasibility study aimed at determining the use of neoadjuvant therapy and randomizing patients based on their response into either organ preservation or local excision arms.

We hope this book appeals to surgeons, surgical trainees, oncologists, radiotherapists and specialist nurse practitioners alike, each closely involved in modern rectal cancer care. We are particularly grateful to all of the chapter authors for their time, expertise, creativity and patience which were essential to the production of this book as it slowly evolved in the face of some recent dramatic changes to world rectal cancer care. When we formulated the book structure, taTME and robotic proctectomy were only just emerging and it became necessary to wait for the initial results of these exciting therapies before sending the book to the publishers. We wish to thank Melissa Morton of Springer for her promotion of the book concept and Vignesh Iyyaduraisuresh and Sargunan Saranya for their design and production of the final volume.

Los Angeles, CA, USA — Mary Kwaan
Melbourne, Australia/Tel-Aviv Israel — Andrew Zbar
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Contents

Contributors

Zaid Abdelsattar, MD, MS Mayo Clinic, Rochester, MN, USA

Osama Al-Bermani, B.Pharm (Hons), MBBS Department of Surgery, The Townsville Hospital, Townsville, QLD, Australia

Nabila Ansari, MBBS, FRACS Department of Colon & Rectal Surgery, Royal Prince Alfred Hospital, Sydney, NSW, Australia

Maria Clara Arroyave, MD Department of Surgical Oncology, AIS Channel, Clinica Somer, Rionegro, Colombia

Sarah J. Atkinson, MD Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

S. Balyansikova, MD, PhD Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, UK

Pablo Bejarano, MD Department of Pathology and Laboratory Medicine, Cleveland Clinic Florida, Weston, FL, USA

A. Belli, MD, PhD Istituto Nazionale Tumori - "Fondazione G. Pascale" - IRCCS, Napoli, Italy

Mariana Berho, MD Department of Pathology and Laboratory Medicine, Cleveland Clinic Florida, Weston, FL, USA

John Beynon, BSc, MBBS, MS, FRCS (ENG.) Singleton and Morriston Hospitals, Swansea, UK

F. Bianco, MD Istituto Nazionale Tumori - "Fondazione G. Pascale" - IRCCS, Napoli, Italy

Jason R. Bingham, MD Department of General Surgery, Madigan Army Medical Center, Tacoma, WA, USA

Ronald Bleday, MD Section of Colon and Rectal Surgery, Brigham and Women's Hospital, Boston, MA, USA

Gina Brown, MBBS, MRCP, FRCR, MD, FASCRS Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, UK

Åsa Collin, MD Department of Surgical Science, Uppsala University, Uppsala, Sweden

S. De Franciscis, MD, PhD Istituto Nazionale Tumori - "Fondazione G. Pascale" - IRCCS, Napoli, Italy

F. Borja de Lacy, MD Department of Gastrointestinal Surgery, ICMDM, AIS Channel, Hospital Clínic, Barcelona, Spain

Sanjeev Dayal, FRCS Basingstoke and North Hampshire Hospital, Hampshire Hospitals Foundation Trust, Basingstoke, UK

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

Martyn D. Evans, BM, MPhil, FRCS (Gen Surg) Singleton and Morriston Hospitals, Swansea, UK

Joakim Folkesson, MD, PhD Department of Surgical Science, Uppsala University, Uppsala, Sweden

Frank A. Frizelle, MBCHB, MMedSci Christchurch Hospital and University Department of Surgery, University of Otago, Christchurch, New Zealand

Bengt Glimelius, MD Department of Immunology, Genetics and Pathology, Uppsala University, University Hospital, Uppsala, Sweden

Rob Glynne-Jones, FRCR, FRCP Mount Vernon Cancer Centre, Northwood, Middlesex, UK

Karyn A. Goodman, MD, MS Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO, USA

Sarah W. Grahn, MD Division of Colon and Rectal Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Ashish Gupta, MD, FRCS Basingstoke and North Hampshire Hospital, Hampshire Hospitals Foundation Trust, Basingstoke UK

Marcia Hall, MBBS, PhD, FRCP Mount Vernon Cancer Centre, Northwood, Middlesex, UK

Antonia Henry, MD Naval Medical Center, San Diego, CA, USA

Alexander G. Heriot, MB BChir, MD, MA, MBA Department of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

University of Melbourne, Melbourne, VIC, Australia

Nir Horesh, MD Department of Surgery and Transplantation, Department of Surgery B, Chaim Sheba Medical Center, Tel Hashomer Hospital, Ramat Gan, Israel

Yik-Hong Ho, MBBS(Hons), MD, FRCSEd, FRCS(Glasg) Department of Surgery, School of Medicine, James Cook University, Townsville, QLD, Australia

Tracy L. Hull, MD, FACS, FASCRS Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA

Eric H. Jensen, MD, FACS Department of Surgery, University of Minnesota, Minneapolis, MN, USA

J. Joshua Smith, MD, PhD Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Department of Surgery, Weill Cornell Medical College, New York, NY, USA

Deborah S. Keller, MD Division of Colon and Rectal Surgery, Columbia University Medical Center, New York, NY, USA

Rohit Kochhar, MBBS, MD, FRCR, DNB The Christie NHS Foundation Trust, Manchester, UK

University of Manchester, Manchester, UK

Joseph C. Kong, MBBS, FRACS, PhD Department of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Fumio Konishi, MD Department of Surgery, Nerima Hikarigaoka Hospital, Tokyo, Japan

Tsuyoshi Konishi, MD, PhD Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Antonio M. Lacy, MD, PhD Department of Gastrointestinal Surgery, ICMDM, IDIBAPS, CIBEREHD, AIS Channel, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

Ryan M. Lanning, MD, PhD Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO, USA

Christopher J. LaRocca, MD Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Emil Lou, MD, PhD Department of Medicine, Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA

Ann C. Lowry, MD Division of Colon and Rectal Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Prakash Manoharan, MBChB, MRCP, FRCR The Christie NHS Foundation Trust, Manchester, UK

University of Manchester, Manchester, UK

Francois Mauvais, MD Department of Digestive Surgery, Beauvais General Hospital, Beauvais, France

Justin A. Maykel, MD Department of Surgery, Division of Colon and Rectal Surgery, University of Massachusetts Medical School, Worcester, MA, USA

Jacob McCormick, MBBS, FRACS Christchurch Hospital and University Department of Surgery, University of Otago, Christchurch, New Zealand

F.D. McDermott, MD, FRCS Royal Devon & Exeter Hospital, Exeter, UK

Brendan J. Moran, MCh, FRCS, FRCSI Basingstoke and North Hampshire Hospital, Hampshire Hospitals Foundation Trust, Basingstoke, UK

Y. Nancy You, MD Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Lars Påhlman†, MD, PhD Department of Surgical Science, Uppsala University, Uppsala, Sweden

Pranavan Palamuthusingam, MBBS Department of Surgery, The Townsville Hospital, Townsville, QLD, Australia

Ian M. Paquette, MD Department of Surgery, Division of Colon and Rectal Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Felipe Quezada-Díaz, MD Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Elizabeth R. Raskin, MD Department of Surgery, Loma Linda University Health, Loma Linda, CA, USA

Scott Regenbogen, MD, MPH University of Michigan, Ann Arbor, MI, USA

Jean-Marc Regimbeau, MD, PhD Department of Digestive Surgery, Amiens University Hospital, Amiens, France

G.M. Romano, MD Istituto Nazionale Tumori - “Fondazione G. Pascale” - IRCCS, Napoli, Italy

Charles Sabbagh, MD, PhD Department of Digestive Surgery, Amiens University Hospital, Amiens, France

Tarik Sammour, MBChB, PhD Colorectal Unit, Royal Adelaide Hospital, University of Adelaide, Adelaide, SA, Australia

M.R.S. Siddiqui, MBChB, MRCS Department of Colorectal Surgery, Croydon University Hospital, Croydon, Surrey, UK

Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, UK

N.J. Smart, MD, FRCS Royal Devon & Exeter Hospital, Exeter, UK

Erica B. Sneider, MD Department of Surgery, Division of Colon and Rectal Surgery, University of Massachusetts Medical School, Worcester, MA, USA

Michael J. Solomon, MBBCh(Hons), BAO, MSc Royal Prince Alfred Hospital, Camperdown, NSW, Australia

RPAH Medical Center, Newton, NSW, Australia

Scott R. Steele, MD, FACS, FASCRS Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA

Ishwaria Subbiah, MD Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Todd M. Tuttle, MD Division of Surgical Oncology, University of Minnesota, Minneapolis, MN, USA

Michael A. Valente, DO, FACS, FASCRS Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA

D.C. Winter, FRCSI, MD, FRCS (Gen) Department of Surgery, St Vincent's University Hospital, Dublin, Republic of Ireland

Andrew P. Zbar, MD (Lond), MBBS, FRCS (Ed) University of Melbourne, Melbourne, VIC, Australia

Department of Surgery and Transplantation, Department of Surgery B, Chaim Sheba Medical Center, Tel Hashomer Hospital, Ramat Gan, Israel

Department of Anatomy and Neuroscience, The University of Melbourne, Parkville, VIC, Australia

Part I
Epidemiology

Chapter 1
The Epidemiology of Rectal Cancer

Ian M. Paquette and Sarah J. Atkinson

Introduction and General Demographic Considerations

In the United States, colorectal cancer (CRC) is the third most common cancer in men and the second commonest cancer in women (746,000 *vs.* 614,000 cases, respectively in 2012) [1]. There is substantial variability in its worldwide incidence, with the highest incidence seen in developed regions and the lowest incidence recorded in developing regions (Fig. 1.1). The highest incidence is reported in Australasia (44.8 cases per 100,000 males), whereas males in Western Africa have the lowest incidence (4.5 per 100,000) and where geographic variability is reflective of inherent lifestyle differences. In 1969, Denis Burkitt made the observation that populations in low risk areas had an overall higher dietary fiber intake with a greater stool bulk and a more rapid colonic transit time when compared with Westernized countries [2]. Although controversial, the suggestion was that fiber depletion (as well as exposure to more refined carbohydrates) promoted carcinogenesis, however, there have been other later epidemiological studies which have failed to support Burkitt's original hypothesis [3]. Despite this, the concept is supported by data showing that patients who migrate from areas of low to high incidence tend to develop the same incidence of CRC as their new adopted environment, [4] implying a potential role for dietary primary CRC prevention.

Though most data sources present epidemiologic data on colon and rectal cancer as a single entity, the Surveillance, Epidemiology and End-Results database (SEER)

I. M. Paquette (✉)
Department of Surgery, Division of Colon and Rectal Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA
e-mail: ian.paquette@uc.edu

S. J. Atkinson
Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

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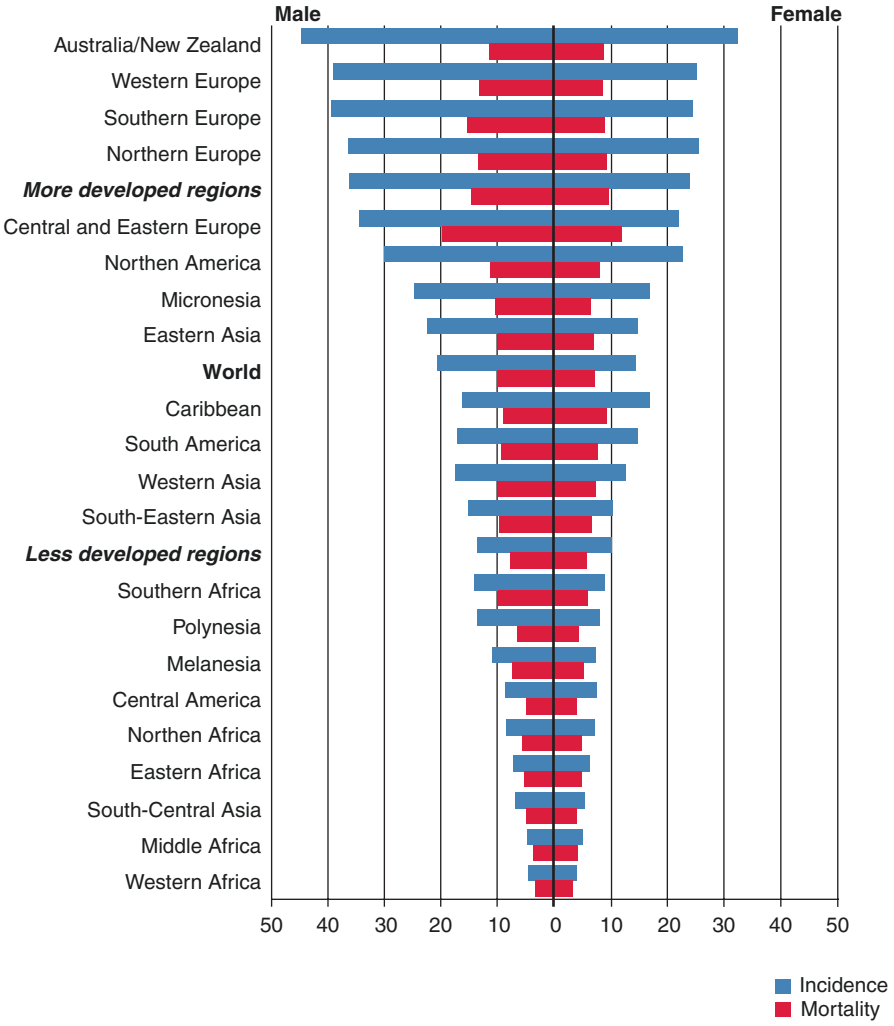

Fig. 1.1 Incidence of colorectal cancer worldwide. (WHO International Agency for Research on Cancer)

from the National Cancer Institute (NCI) allows for a more precise quantification of the burden imposed by rectal cancer alone in the United States, [5] where rectal cancer is strongly associated with age (Fig. 1.2). Though the incidence of rectal cancer begins to rise after age 40, a sharp increase is seen after age 50, with the vast majority (over 90%) of cases being diagnosed in people > age 50 years of age [6–8]. Overall, more than 60% of the cases and 70% of the deaths will occur in those patients over 65 years of age [6].

Over the past decade, there has, however, been a decrease in the incidence of rectal cancer in people age ≥50, with a steady increase in those patients under

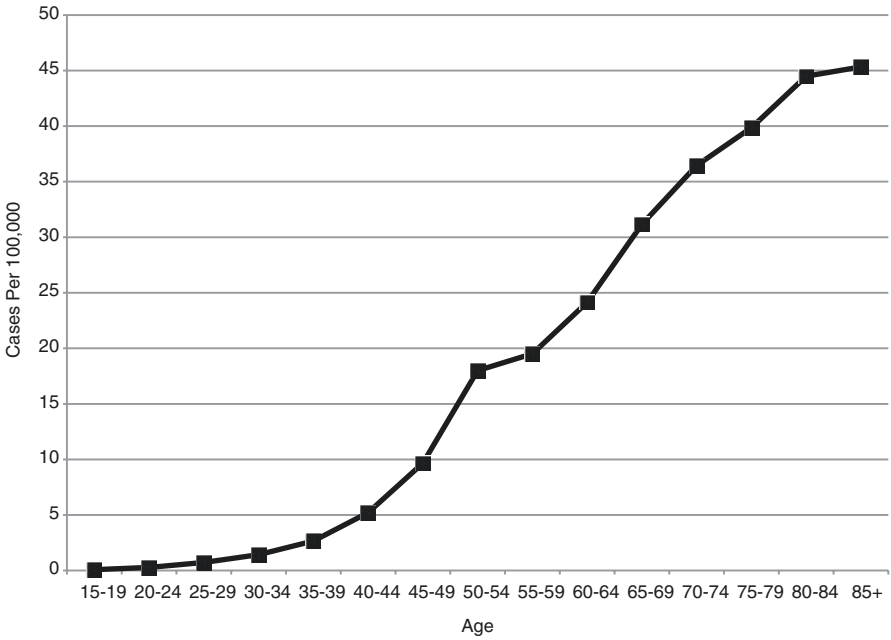

Fig. 1.2 Age-specific incidence of rectal cancer. (SEER data 2014)

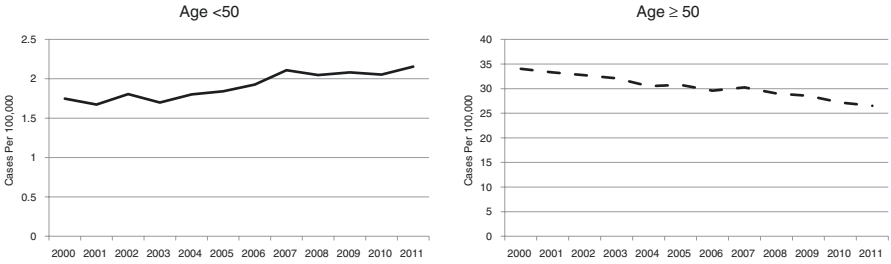

Fig. 1.3 The impact of age (< or > 50 years) on rectal cancer incidence. (SEER data 2014)

50 years of age (Fig. 1.3) [9]. The annual percentage change in incidence continues to rise at approximately 1.8% per annum in individuals < age 50 with a decrease of 1.5% per annum observed in the 50–64 year age group and a 4.5% decrease in the annual percentage change in the 65 year and older age group. A major potential reason for this declining incidence in older patients is the increased use of screening colonoscopy and sigmoidoscopy in this age group, [10] although this has demonstrated only a change in left-sided CRC deaths in those undergoing full colonoscopy without an effectiveness for right-sided cancers [11–13]. A more alarming trend, however, demanding of further research, is the reasons for this precipitous increase

in rectal cancer incidence in the younger patient. In this regard, similar data has been shown in the high prevalence area of New Zealand where the incidence of rectal cancer has increased by 18% in men and 13% in women between 1995 and 2012 particularly in those under 50 years of age [14].

Gender and race are also both strongly associated with the varying incidence of rectal cancer where it is generally about 25% higher in men when compared with women [15] and where African Americans (AA) have a markedly higher incidence when compared with the Caucasian population (Fig. 1.4) [5]. This disparity in incidence between the AA and white populations is further increased if cases of colonic cancer are also included, where there are numerous reports demonstrating a more proximal distribution of CRC in the AA subgroup [16–19].

Within the United States itself, there is substantial variability in the incidence of CRC with an incidence <35/100,000 in states such as New Hampshire, Idaho, Arizona, Colorado, and Utah, when compared with states such as Mississippi, Kentucky, and Louisiana, where there is an average incidence >50 cases per 100,000 [20]. With respect to this finding the CRC incidence correlates with lifestyle choices where those regions with a higher prevalence of smoking and obesity have the higher CRC rates and where those regions actively participating in CRC screening protocols, which engage in leisure-time physical exercise activity and who eat at

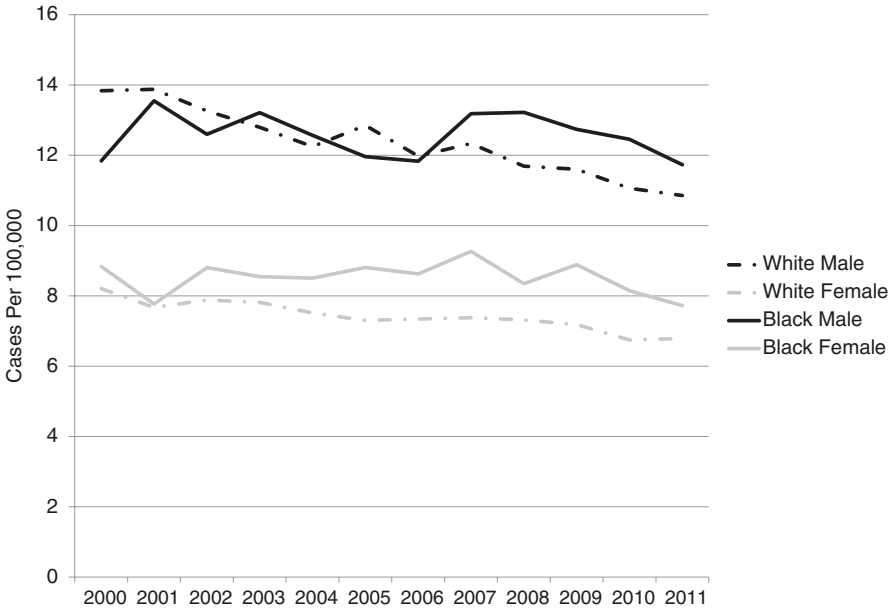

Fig. 1.4 Rectal cancer incidence: effect of gender and race

least 5 or more fruits and/or vegetables per day have the lowest recorded CRC incidence [21].

By contrast, survival in rectal cancer is largely dependent upon the stage at presentation, with 88% of patients who present with localized disease surviving 5 years vs. 69.5% with regional disease and 12.9% presenting with distant disease [8]. This standard view should be tempered with the fact that over the past 3 decades rectal cancer survival has dramatically increased when, from 1975 to 77 for example, the 5-year survival for all stages was around 48% [7, 8]. This statistic increased to 58% overall between 1987 and 1989 and to 68% in the period between 2003 and 2009 [7, 8]. In this respect, since 1975, there have been absolute increases in the 5-year survival of 12%, 14.4%, and 7.2%, respectively for localized, regional and distant stages of rectal cancers [8] which most likely reflects the multifactorial effects of ongoing improvements in surgical technique [22, 23], pathologic assessment, [24] the timing and the appropriate selection of radiation therapy, [25, 26] general advances in chemotherapy and the institution of multidisciplinary team management [27]. Though patients with colon cancer have historically experienced better 5-year survival than those with rectal cancer, rectal cancer patients now experience at least an equal, if not a better 5-year survival when compared with their colon cancer counterparts (Fig. 1.5).

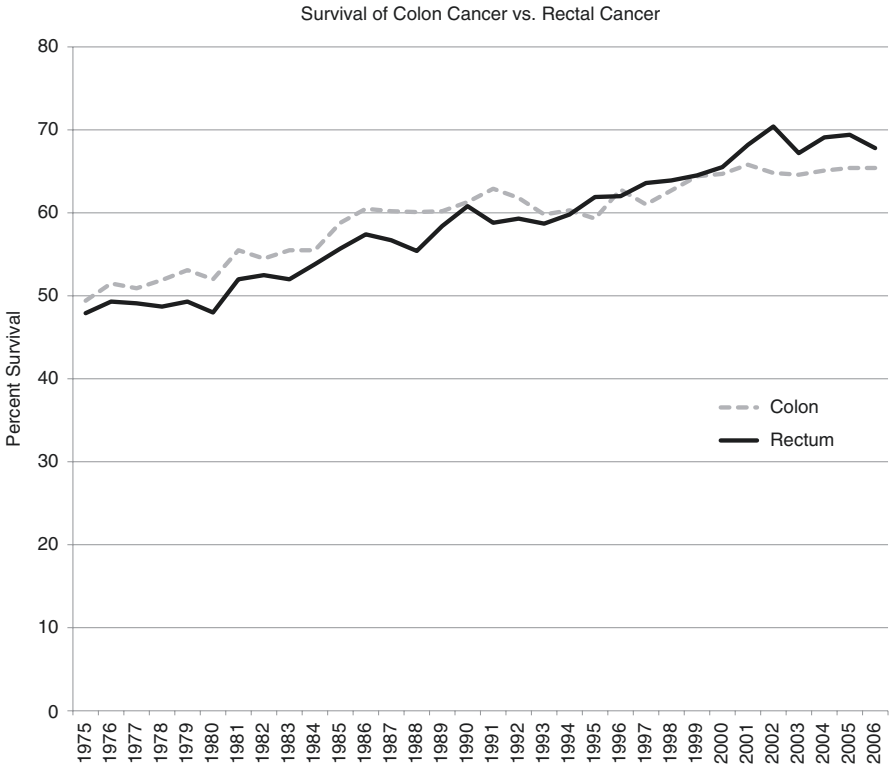

Fig. 1.5 5-year cancer-specific survival: colon vs. rectal cancer

Risk Factors

The majority of studies examining risk factors also include CRC cases as a single entity. In contrast, Wei et al. used data from the Nurses Health Study and the Health Professionals Follow Up Study in order to examine fundamental differences in risk factors between colon and rectal cancer [28]. In this work, the majority of risk factors, most particularly dietary factors, were similar in both types of cancer, however, colon cancer was more strongly associated with a positive family history and a history of consistent physical exercise was more likely preventative of colon cancer than of rectal cancer.

Dietary Components

Numerous studies have suggested a protective effect of a diet high in fiber, fruits and vegetables and low in fat [29–32] with a reduction of the relative risk of developing CRC by 50% in those patients with a high intake of fruits, vegetables and fiber [33]. Part of the difficulty with collection of this type of data is that CRC is a multifactorial process without the availability of randomized cause-related data with all of the results concerning diet produced from observational studies. A limited assessment of the components is discussed below.

Fruit and Vegetable Intake

There have been a large number of studies demonstrating a lower incidence of CRC in populations with an overall higher fruit and vegetable intake. Slattery et al. [31] using data from the state of Utah and the Kaiser Permanente Health System records in California, examined the impact of fruit and vegetable intake on the development of rectal cancer and showed that rectal cancer was inversely associated with the intakes of vegetables (OR = 0.72), fruit (OR = 0.73) and whole-grain products (OR = 0.69), whereas a high intake of refined grains was associated with an increased total cancer risk (OR 1.42). In this analysis, a threshold of 5 servings of vegetables per day was needed in order to detect a specifically reduced overall risk of rectal cancer. Similarly, Terry et al. [32] examined a cohort of 61,463 women and determined that the individuals who consumed the lowest amounts of fruits and vegetables (<1.5 servings per day) had a relative risk of 1.65 for the development of all CRC. In this regard, a pooled analysis by Koushik et al. [33] of 14 cohort studies which included 756,217 people, showed that the total fruit and vegetable intake was associated with a decreased CRC risk of the distal large bowel, (RR = 0.074) but not of the proximal colon. Other studies by contrast, such as the Health Professionals Follow-up Study and the Cancer Prevention Study II Nutrition Cohort failed to show any reduction of CRC risk with a high fruit and vegetable intake [34, 35].

Fat

Countries with populations consuming a high fat diet generally have a higher rate of CRC when compared with those countries whose populations consume lower fat diets [36]. This traditional statistical association may, however, be confounded by many other factors including the dietary fiber intake, the amount of alcohol ingested and the exercise levels of the considered cohorts and the current data are conflicting. Howe et al. [37] summarizing 13 case-control studies which evaluated the relationship between total energy, total fat, fat components, and total cholesterol found no energy-independent effects of the total fat intake on the overall CRC risk. Equally, the Women's Health Initiative [38] in a large randomized controlled trial, examined the CRC incidence between those women randomized to a low fat diet and their control group with no dietary modifications and over a mean follow-up of 8.1 years also found no difference in the overall CRC incidence (RR = 1.08, 95% CI [91–1.29]). In this respect, there have also been two prospective controlled trials, one of which identified a small association between dietary fat and CRC incidence and another that found no such association [39, 40].

Red Meat

Several prospective studies in the United States have demonstrated positive associations with red or processed meat intake [41, 42]. Concerning this effect, the high iron content of red meat increases the free radical production and N-nitroso compounds in the colon which have been shown to induce chronic mucosal damage and which are carcinogens in animal models [43]. The Shanghai Women's Health Study [44] prospectively investigated the association between dietary nitrates and nitrites (precursors of N-nitroso compounds) by the analysis of detailed food questionnaires and over a mean follow-up of 11 years in 73,118 participants identified 619 cases of CRC with no specific association between nitrite intake and CRC risk.

A meta-analysis of red meat consumption in Western countries by Norat et al. [45] found that a high intake of red meat was associated with a moderate increase in the overall CRC risk with the Health Professionals study [46] showing a similar results particularly for the distal colon. In this regard, Larsson et al. [47] conducted a prospective study of 7367 and concluded that the relative risk for CRC of those participants who consumed the most red meat relative to those who consumed the least was 1.28 overall (95% CI 1.15–1.42). In this study, a subset analysis of 3 studies which specified colon cancer by location found that red meat increased the risk of distal but not proximal cancers. In order to control for other dietary factors, a secondary analysis in this study was restricted to studies that adjusted for physical activity, BMI, smoking, alcohol, energy expenditure and calcium intake and with these adjustments and corrections, the relative risk for CRC in those people with the highest red meat intake compared with the lowest red meat intake was overall 1.29 (95% CI 1.09–1.53).

Fiber

As already mentioned, the initial association between CRC risk and dietary fiber was suggested by African studies from Burkitt [2, 48] who theorized about the fiber protective effects in primary CRC prevention. This data has been brought into stark reality with a recent large systematic analysis failing to show a clear association between dietary fiber intake and the incidence of recurrent colorectal precursor adenomas over an 8-year minimum follow-up period [49]. The Burkitt thesis is that fiber increases the intestinal transit reducing the exposure time to potential ingested carcinogens with a recommended level of crude fiber intake for a standard Western diet. Since Burkitt's landmark work, studies examining the relationship between dietary fiber intake and CRC development have, however, been quite inconsistent with Slattery et al. [31] reporting an inverse association with CRC risk (OR 0.54) although this relationship was strongest for people diagnosed after the age of 65 years. Similarly, a prospective cohort of 500,000 people across 10 separate European countries [50, 51] found fiber to be protective with a 25% reduction in the overall incidence of CRC amongst those who consumed the most fiber relative to those who consumed the least. In the analyses by this same group, the protective effect was greater for the colon than for the rectum.

An analysis of the combined results of 13 prospective cohort studies which included 725,628 males and females by Park et al. [52] also found that increased dietary fiber was associated with a lower incidence of CRC, however, when controlling for all other dietary factors, the result was no longer statistically significant. Equally, two large American cohort studies, the Nurses Health Study and the Health Professionals Follow-up Study, found no relationship between fiber intake and the overall CRC risk [5, 46, 53]. For consideration, the available data has used multiple different types and sources of fiber with varying research methods and although it is certainly possible that fiber alone may not be protective of CRC, there still may be a secondary benefit in conjunction with a healthier diet and lifestyle. Better defined randomized trials with appropriately long-term follow-up will be needed in order to conclusively demonstrate a benefit.

Calcium and Vitamin D

Within the general population, there are several studies which have demonstrated associations between total calcium intake and CRC. The Swedish Mammography cohort for example, [54] found an inverse trend between calcium intake and CRC risk and the Nurses' Health Study and the Health Professionals Follow-Up Study also both found an inverse but non-significant association between the total calcium intake and the prevalence of distal colon cancer. Pooled analysis done by Hjartaker et al. [55] for these two cohorts also calculated a significant inverse trend.

This issue is complex, however, where further study of a United States female cohort that differentiated between dietary calcium and supplements found that dietary calcium was associated with decreased proximal colon cancer but there was

no association for total calcium and CRC overall [56]. In a pooled analysis of 10 cohort studies that included the dietary habits of 534,536 people, dietary calcium intake was inversely associated with overall CRC risk [RR = 0.86, 95% CI (0.78–0.95)] when the highest and lowest intake quintiles were directly compared [57]. In this systematic analysis, the effect was preserved for overall calcium intake (diet plus supplements) with a relative risk of 0.78 (95% CI 0.69–0.88).

When assessing those patients with previous adenomas, a recent Cochrane meta-analysis of two RCTs found that the use of supplemental elemental calcium was associated with a reduction in recurrent colorectal adenomas, (OR = 0.74, 95% CI 0.58–0.95) however, the follow-up for these patients was only 3–4 years, providing insufficient time for colorectal adenoma development and repeat endoscopic assessment [58]. Given that several of the studies surrounding calcium also involved vitamin D supplementation, analyses were later conducted examining whether there was any association between vitamin D alone and CRC risk. In this respect, a 2014 meta-analysis of outcomes associated with vitamin D found an inverse association between the patients' measured vitamin D levels and their overall CRC risk [59, 60].

Folate

Folate plays an integral role in DNA methylation and in gene expression, with initial epidemiologic studies demonstrating an inverse relationship between folate intake and CRC risk [61–64]. Despite this, further studies have failed to find any such association where a 2013 meta-analysis of 7 relevant randomized trials including 33,824 patients found that folic acid supplementation had no significant effect on overall CRC risk (RR = 1.01, 95% CI 0.82–1.23, p = 0.95). It is noted that folate supplementation may have a potentially adverse effect in patients with a prior history of adenomatous polyps where a study published in 2008 found that such patients randomized to 1 mg of folic acid daily had a 44.1% incidence of an adenoma at follow-up compared with 42.4% in the placebo group [65]. This group reported that those patients with serum folate levels in the upper third and fourth quartiles had an increased risk of CRC and that patients who received folate supplementation also had a trend toward a higher incidence of advanced adenomas as well as a higher incidence of ≥3 adenomas overall. In this regard, a case-control study published in 2014 also found that in patients who already have adenomatous polyps, that high serum folate levels correlate with a higher overall CRC risk, without a commensurate CRC risk in healthy controls [66].

Alcohol

Alcohol is one of the few dietary interventions that has been shown to have a stronger effect in rectal cancer than in colon cancer, with several seminal supporting studies. A 2007 meta-analysis of over 6300 patients with CRC in 16 prospective

cohort studies found that a high alcohol intake was significantly associated with an increased risk of rectal cancer (RR = 1.63, 95% CI 1.35–1.97) relative to those patients with the lowest alcohol intake [67]. The European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) trial also examined baseline lifestyle and dietary information, following 478,732 patients for a median of 12 years and this group calculated a relative CRC risk of 1.44 for when comparing the heaviest drinkers to non-drinkers with clear evidence of a dose-risk relationship [68]. In a separate analysis specifically addressing alcohol and rectal cancer, Ferrari et al. [69] showed higher hazard ratios for rectal cancer (HR = 1.12, 95% CI 1.06–1.18) than for either distal colon cancer (HR = 1.08, 95% CI 1.01–1.16) or proximal colon cancer (HR = 1.02, 95% CI 0.92–1.12).

Aspirin

Both invasive and pre-invasive colorectal adenomas induce COX-2 over-expression so that COX-2 suppression has been formally examined in association with CRC risks [70]. Equally aspirin specifically inhibits COX-1, COX-2, prostaglandins and thromboxanes whilst at the same time inducing cellular apoptosis and retarding angiogenesis. Concerning these effects, the Women's Health Study, [71] a randomized controlled trial conducted in 39,876 women aged 45 years and older, randomized patients to either receive 100 mg of alternate day aspirin or a placebo. Observational follow-up at a median of 10 years found that CRC was reduced in the group randomized to receive aspirin (HR = 0.80, 95% CI 0.67–0.97, P = 0.021) with the greatest effect on proximal CRC incidence after the 10 year mark. There were, importantly however, an increased number of both gastrointestinal bleeds in the aspirin-treated group (HR = 1.14, 95% CI 1.06–1.22, P < 0.001) and symptomatic peptic ulcers (HR 1.17, 95% CI 1.09–1.27, P < 0.001).

Further analysis of 2 large randomized controlled trials in the United Kingdom found that patients randomized to aspirin had a reduced incidence of CRC (HR = 0.74, 95% CI 0.56–0.97, P = 0.02) with a greater effect in those patients on aspirin for at least 5 years or more (HR = 0.63, 95% CI 0.47–0.85, p = 0.002) [72]. This study should be viewed with caution with the caveat that the reduced incidence of CRC was only consistently seen after a latency of 10 years of treatment and only in patients who took 300 mg or more of aspirin daily.

A Cochrane review of 3 pooled randomized controlled trials examined the recurrence rates of sporadic adenomatous polyps and found that aspirin significantly reduces the overall recurrence rate (RR = 0.77, 95% CI 0.61–0.96), however, in this study there were no differences in the long term CRC-related outcomes [73]. Similarly, the Physicians Health Study, (a large, randomized controlled trial of aspirin versus placebo in healthy individuals), found no significant reduction in CRC with aspirin usage (RR = 1.15, 95% CI 0.80–1.65) [74]. As a consequence of conflicting studies as well as because there is a reported increase in adverse events amongst aspirin users, the U.S. Preventive Services Task Force does not recommend aspirin usage for CRC prevention in average risk patients.

Obesity

Several studies have found that indexes of abdominal obesity, such as waist circumference or waist-hip ratio, are more sensitive than body mass index (BMI), in defining the relative risk for CRC although in general, these indices are frequently not available in many reported studies [68, 75–79]. The most robust literature concerning an association between CRC and obesity is available for patients with a BMI exceeding 30 where a 2007 meta-analysis examined 31 studies and found that the relative risk of CRC was 1.19 (95% CI 1.11–1.29) for patients with a BMI $\geq$ 30 when compared with those patients with a BMI < 25 [80]. The association detected in this study was even stronger when specifically examining central obesity with a relative risk of 1.45 when comparing the highest to the lowest central obesity rates (95% CI 1.31–1.61).

Several studies have found that the relationship between obesity and CRC may depend on gender with a meta-analysis of 30 prospective studies from North America and Europe showing an increased risk of CRC with a BMI exceeding 30, and with a particularly strong association in men [77]. This gender-dependent association appears to also be preserved when examining the relationship between obesity and rectal cancer with both Larsson's 2007 meta-analysis [77] and a 2009 review by Harriss et al. [80] finding that a BMI $\geq$ 30 is positively related to rectal cancer incidence specifically in men but not in women. The EPIC study which also examined obesity and its relationship with colon and rectal cancer separately within each sex, found in a multivariate model stratified by center and adjusted for age, sex, education and lifestyle factors, that there was a calculated hazard ratio of 0.90 (95% CI 0.77–1.05) for men with a BMI < 25 and a waist circumference < 94 cm [68]. In this analysis, their calculated hazard ratio for women within the same multivariate model was 0.95 (95% CI 0.81–1.12) for a BMI < 25 and a waist circumference < 80 cm.

Hormonal differences may play a part in the gender-dependent association between obesity and CRC risk where the Million Women Study examined the role of obesity and CRC risk separately in pre and post-menopausal women [81]. This study found that increasing BMI was associated with CRC specifically in premenopausal women with a RR of 1.61 (95% CI 1.05–2.48) whereas in the postmenopausal group, there was no detectable association.

Physical Activity

A sedentary lifestyle has been implicated in a number of different diseases and while there are studies that find increased activity to decrease CRC risks, the exact benefit is difficult to quantify since increased activity levels may be more likely in individuals with other healthy lifestyle factors such as diet and the avoidance of tobacco. Nilsen and Vatten prospectively analyzed the association between CRC and physical activity in 75,219 Norwegian men and women and found a negative association [82]. When those participants with the highest activity level

were compared with those with the lowest, the age-adjusted relative risk was 0.54 (95% CI 0.37–0.79). A meta-analysis of CRC risk factors by Johnson et al. [83] examining this effect also found that physical activity was inversely associated with CRC risk (RR = 0.88, 95% CI 0.86–0.91 for 2 standard deviations increase in physical activity score). Overall, these findings are consistent across the literature where in general greater physical activity appears to be associated with a reduced overall CRC risk, however, in those studies which differentiate colon from rectal cancer, the association seems to be much clearer only for colonic tumors [80, 84–86].

The NIH-AARP study also found a non-significant trend towards a reduced risk of rectal cancer in more active men, however there was no such protective effect observed in women [87]. Since increased activity levels are often part of a healthier overall lifestyle, the EPIC cohort (European Prospective Investigation into Cancer and Nutrition) collected dietary and lifestyle information in an effort to try and analyze the synergistic effects of multiple healthy lifestyle choices [68] collecting data concerning diet and lifestyle habits at a baseline point and after a median follow-up time of 12 years, during which 3759 incident CRC cases were identified. In this study by Aleksandrova et al. there was no association between physical activity levels alone and the incidence of rectal cancer, however, participants with 2 healthy lifestyle indices had an HR of 0.90 (95% CI 0.74–1.11). Those with 3 indices had an HR of 0.80 (95% CI 0.66–0.97), 4 indices an HR of 0.70 (95% CI 0.57–0.85) and 5 indices an HR of 0.68 (95% CI 0.53–0.88). All of these associations were stronger in men than in women.

Smoking

Multiple studies have found stronger associations between smoking and rectal cancer than for smoking and colon cancer. A meta-analysis of 36 studies found that relative to non-smokers, current and former smokers had an increased CRC incidence along with a dose-dependent association [88]. Of those studies that separated rectal and colon cancer, the association was twice as strong for rectal lesions, although neither reached statistical significance. The Women's Health Initiative study also revealed a significant association between rectal cancer risk and cigarette smoking (RR = 1.95; 95% CI 1.10–3.47) but there was no significant association with colon cancer [89]. In this regard, a meta-analysis by Botteri et al. [90] reviewed 106 observational studies and pooled the adjusted risks in 26 of the studies, calculating a RR of 1.18 (95% CI 1.11–1.25) for smokers and CRC when compared with those who had never smoked. In this study, the risk estimates were also higher for rectal than for colon cancer amongst current smokers (P = 0.02). Another meta-analysis by Tsoi and colleagues [91] of 28 American, European and Asian prospective studies found that current smokers had a modestly higher risk of CRC overall (RR 1.20, 95% CI 1.10–1.30) when compared to never smoker cohorts and that rectal cancer was more closely associated with a history of smoking (RR 1.36, 95% CI 1.15–1.61).

Inflammatory Bowel Disease

The special group of patients with long-standing ulcerative colitis (UC) are known to be at increased risk for CRC secondary to the inflammatory state and environment in the colon with the precursors of dysplasia and dysplasia-associated lesions or masses (DALM) [92]. A 2001 meta-analysis by Eaden et al. [93] calculated the incidence rates from 116 studies where the cumulative probability of CRC was 2% by 10 years after the disease onset, 8% by 20 years and 18% by 30 years. The overall prevalence of CRC in any UC patient in this study was 3.7%. A 2012 meta-analysis of 8 population-based cohort studies found a pooled standardized incidence ratio of 2.4 (95% CI 2.1–2.7) for patients with UC and also found that male gender, young age at UC diagnosis and extensive colitis increased the overall risk [94]. Other studies have also cited the extent of the disease as a factor influencing the risk of CRC in UC patients, with a population-based study in Sweden showing that patients with pancolitis had a CRC incidence ratio of 14.8 (CI 11.4–18.9) when compared with the expected incidence within their individual cohort [95].

The relationship between Crohn's disease and CRC is less consistent but Ekbom's Swedish population-based study [95] found an increased risk in Crohn's patients (RR 2.5, 95% CI 1.3–4.3), especially amongst those whose Crohn's disease was confined to their colon (RR 5.6, 95% CI 2.1–12.2). A Canadian population-based cohort study by Gillen et al. [96] also examined the association between Crohn's disease and rectal cancer but found no increased risk, although this group did find an association between Crohn's disease and colon cancer (incidence rate ratio = 2.6, 95% CI 1.69–4.12).

Family History

Between 3 and 6% of all CRC's are attributed to inherited familial syndromes, such as Lynch syndrome, Familial Adenomatous Polyposis, and hamartoma syndromes [97] although family history remains an important risk factor even outside of these defined genetic syndrome disorders. These specific disorders like hereditary non-polyposis CRC (HNPCC) represent specific mutations in genes implicated in the DNA repair pathway (the MLH1 and MSH2 genes) with FAP caused by a mutation in the tumor suppressor APC gene. HNPCC will account for between 2 and 5% of all CRC's with an average age at diagnosis in the 40's and an overall 70% risk of CRC development along with a host of other extracolonic malignant tumor clusters (uterus, gastric, small bowel, pancreas, kidney and ureter). Patients with a single affected first-degree relative with CRC have a two-fold risk increase for CRC over the general population and this risk increases further if the index case is diagnosed before 50–60 years of age [98]. Early screening is recommended for those people with a family history of polyps in relatives under 60 years of age, however, these recommendations are currently based upon self-reporting of polyp history and may thus be inaccurate [99, 100].

Summary

Several dietary and lifestyle components have been linked to the development of rectal cancer. Specifically, gender, race, the consumption of vegetables, whole grains, red meat and alcohol, obesity and the smoking status may be considered as significant risk factors, however, it is accepted that many of the studies reporting these associations are retrospective and underpowered. Future studies examining rectal cancer as a separate entity from colon cancer and defining the relative risk of different lifestyle choices and interventions are clearly needed.

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Part II
Imaging in Rectal Cancer

Chapter 2
Endorectal Ultrasound

Martyn D. Evans and John Beynon

Endorectal ultrasound (ERUS) since its introduction over 30 years ago has refined the preoperative staging of rectal cancer. Initially used to image the prostate and rectum the primitive 4 megahertz (MHz) transducers have progressed to higher frequency probes with markedly better resolution and most recently with the routine addition of three-dimensional (3D) machines. This chapter addresses the applications of ERUS in the preoperative staging of rectal cancer and its place alongside other modalities such as MRI.

The History and Development of Endorectal Sonography (ERUS)

The first recorded application of ERUS was by Wild and Reid in 1952, with their development of an "echoendo probe" [1–3]. This probe with its ellipsoidal sound head containing the piezoelectric crystal was mounted onto a hand-held flexible shaft which contained a drive shaft and a drive motor. As with most designs, subsequently the transducer was covered by a water-filled balloon which transmitted the sound beam at right angles to its long axis. This advance though resulted in the production of rigid shaft endoprobes similar to those used currently. In this design, a rigid shaft also allows introduction into the rectum through a proctoscope. The images are then produced for each revolution of the sound head within the rectum and this early system clearly demonstrated a crude, layered image of the normal bowel and subsequently a similarly first rudimentary image of a rectal cancer. It was nearly 30 years later largely hampered by technical limitations before this approach

M. D. Evans · J. Beynon (✉)
Singleton and Morriston Hospitals, Swansea, UK
e-mail: martdoc@doctors.net.uk; johnbeynon56@doctors.or.uk

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was applied in a clinical setting when Dragsted and Gammelgaard evaluated 13 cases of rectal cancer in 1983 [4].

This group used a Bruel and Kjaer ultrasound scanner Type 8901 and a rigid probe equipped with a 4.5 MHz transducer (initially designed for prostatic imaging) and compared the pre-operative ERUS with postoperative histopathology. The extent of invasion was correctly predicted in 11 cases although the quality of the images remained relatively poor.

Technological advances since then have allowed more detailed imaging and therefore greater accuracy. The plane of scanning can now be either transverse or longitudinal and there are some instruments that are able to scan in both planes. For the surgeon the advantage of images produced by a radial scanner are that they can be directly compared with the operative appearance when looking down into the pelvis at surgery. These 360-degree images can only be produced by mechanically rotating probes which all require a water-filled balloon to cover the transducer for acoustic contact. The balloon distends the rectum, preventing distortion by in folding and making interpretation easier as the area being scanning is more likely to be within the optimal focal range of the transducer. The only limitation of the technique is that stenosis will occasionally prevent full evaluation of the lesion as it may not be possible to scan the complete length of the rectum or traverse the entire length of the tumor and detect lymph nodes lying rostrally.

Most units publishing data concerning the efficacy of ERUS (which really became a viable option for staging in the mid 1980s) have used equipment produced by Bruel and Kjaer (Denmark: Probe type 1850) in conjunction with a 5.5–7 MHz transducer and more recently with a 10 MHz probe. In most series, the 7 MHz transducer (focal length 2–5 cm) had been the probe of choice. For the best imaging, the rectum should be clear of faeces which can simply be accomplished with a disposable enema or suppositories. Examinations have traditionally been performed with the patient in the left lateral position with the endoprobe either introduced blindly or through a proctoscope. This latter method can be an advantage when examining higher or stenotic lesions to ensure that the transducer has traversed the tumour extent. Following insertion, the balloon is inflated and the transducer switched on. Then the probe is moved proximally and distally to scan the area of interest. To obtain optimum images, both the position of the probe and the volume of water in the balloon can be altered. This allows as has been mentioned above for the area of interest to lie within the optimal focal range.

The endosonographic appearance of the rectum is unique. The rectum has five distinct ultrasonic layers which in essence correspond to the histological layers of the rectal wall, with three hyperechoic layers separated by two hypoechoic layers as extensively described (Fig. 2.1) [5]:

First Hyperechoic layer—Interface between the water/balloon and the mucosal surface

Second Hypoechoic layer—Combined image produced by the mucosa and muscularis mucosae

Third Hyperechoic layer—Submucosa

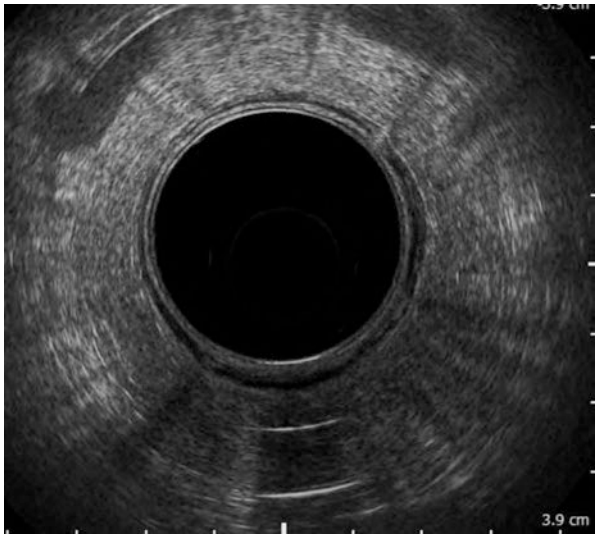

Fig. 2.1 The five layer structure of the rectal wall as seen on ERUS

Fourth Hypoechoic layer—Muscularis propria
Fifth Hyperechoic layer—Interface between the muscularis propria and perirectal fat or serosa if present.

Occasionally a seven layered image is seen as the transducer can differentiate the two parts of true muscle layer of the rectum i.e. the circular and the longitudinal [6].

ERUS can also identify the extrinsic anatomy of the uterus, vagina, prostate and seminal vesicles and evaluate whether congenital fascial planes between the rectum and these structures are intact or infiltrated by tumour.

Three Dimensional Ultrasound

With further technological advances there has been increasing interest in the use of three dimensional (3D) ERUS. This has arisen because of the limitations of viewing a 3D structure as a two dimensional (2D) image; an effect which is best illustrated by the example of a rectal tumour. As only discrete 2D images can be viewed at any moment, no direct imaging of the longitudinal extent of the tumour and its spatial relationships is available so that the series of transverse images must be assimilated by the observer to produce a mental image of the real anatomy [7].

Such 3D imaging is only possible with suitable ultrasound apparatus and integrated computer technology with 3D software [8]. The images are constructed from a synthesis of a high number of parallel trans-axial 2D images stacked on one another with computerized interpolation of the data between axial acquisitions [9].

The resolution of 2D images are measured in pixels (each pixel having an *x* and a *y* plane). In 3D ultrasound the pixel is transformed into a small 3D picture element called a voxel where the depth of the voxel is critical to the resolution of the 3D image. High resolution 3D ultrasound typically acquires four to five transaxial images per 1 mm acquisition of length in the *z* plane [9]. The images are then rendered using one of three basic techniques [8, 9] namely:

1. *A Surface-based viewing technique.* Here, an operator or algorithm identifies the boundaries of the structures to create a wire-frame representation. This technique fails when a strong surface cannot be found such as in the subtly layered structures of the anal canal. In this view the surface of an image is highlighted and the technique has been used in virtual colonoscopy and in foetal representation.
2. *Multiplane viewing techniques.* In this case, three perpendicular planes (axial, transverse and longitudinal) are displayed simultaneously which can be moved and rotated by the operator so as to visualize the lesion at different angles.
3. *Volume render modes.* Here, the 3D image is projected onto a 2D plane by casting rays through the 3D picture where the voxel values intersected by each ray can be multiplied by various parameters defining opacity, luminosity, filtration and image thickness governing the inclusion or exclusion of different pixilated values and then summed to produce different effects. In this case, unlike the surface rendered mode, the image structure inside a defined volume is analyzed like a black box.

The efficacy of 3D over 2D ERUS in the staging of primary and recurrent rectal cancer has been evaluated in recent years [7, 10–12]. In this respect, there is no doubt that 3D imaging has some advantages over 2D techniques although it has not really found its niche and its real advantages remain unclear particularly now that multimodal imaging is available [13].

Endorectal Ultrasound and Rectal Cancer

In the past, surgery for rectal cancer was performed as expediently as possible by blind blunt dissection, yielding relatively poor oncological results with high local failure rates and locoregional pelvic recurrence. In the last three decades, the local failure rates in rectal cancer treatment have markedly reduced [14] all of which has been achieved through improved radiological staging, advances in surgical technique and the use of pre-operative neoadjuvant therapy. Surgically, rectal cancers may be treated by local excision, including Trans Endoscopic MicroSurgery (TEMS), by total mesorectal excision (TME) or by multi-visceral pelvic surgery for the more advanced tumours. Accurate pre-operative local staging (T and N stage) of rectal cancer is therefore critical in order to offer the patient the optimal treatment [15].

In this regard, both ERUS and Magnetic Resonance Imaging (MRI) have become the norm to locally stage rectal cancer, dramatically improving local staging accuracy. Consequently patients diagnosed with rectal cancer today receive a bespoke tailored evidence-based approach to both staging and the treatment of their disease. When planning the patient's management some of the important questions that need to be addressed are:

(a) Is the disease confined to the mucosa and sub-mucosa?
(b) If so, can the disease be successfully managed by local excision without recourse to total mesorectal excision (TME) surgery?
(c) If the tumour has invaded the muscularis propria, are there any indications that the patient should be offered pre-operative neoadjuvant treatment prior to surgical TME in order to ensure a complete mesorectal excision without a likelihood of circumferential radial margin (CRM) involvement?
(d) In more advanced cases is there a likelihood for a multi-visceral resection?
(e) Has neoadjuvant treatment sufficiently downstaged the tumour so that the surgical strategy can be modified or surgery even avoided? (addressed in Chaps. 11 and 12 "Watch and Wait" "ERUS in Advanced Rectal Cancer").

Both MRI and ERUS have established roles in answering each of these specific questions and will be discussed in this chapter with a particular emphasis on ERUS. The role of MR imaging in rectal cancer assessment and in the response to neoadjuvant therapy is considered in a subsequent chapter of this section.

On ERUS, rectal tumours have a typically hypoechoic appearance where as the tumour invades deeper through the rectal wall, the normal sonographic anatomy becomes disrupted [16, 17]. By comparing the changes caused by a tumour with the normal sonogram the depth of tumour and hence an ultrasound T stage (denoted with the "u" prefix) [18, 19] can be assigned to the tumour (Table 2.1) [20] (Figs. 2.2, 2.3, 2.4, 2.5, and 2.6).

ERUS in Early Rectal Cancer

Patients with early mucosal disease without lymphatic involvement may be considered for endoscopic polypectomy, trans-anal excision or TEMS. The proportion of patients diagnosed with early stage disease has increased with the widespread introduction of population-based screening [21] and the National Bowel Screening Programme UK in 2006. The latter programme has resulted in the earlier detection of rectal tumours and highlighted less aggressive treatment modalities for management. In this situation ERUS has been found on multivariate analysis of 16 years of scientific literature to have a sensitivity of 94% and a specificity of 86% in determining invasion of the muscularis propria [19]. When comparing ERUS with MRI, the same meta-analysis found that the sensitivity of ERUS is equivalent to that of MRI but that the specificity of ERUS is superior (86 *vs.* 69%, respectively). These modalities are being used routinely in an environment where the indications for

Table 2.1 American Joint Council on Cancer (AJCC) T staging of rectal cancer [20]

TNM T Stage	Histopathology	Ultrasonographic features
Tx	Primary lesion cannot be assessed	Tumour depth not determined
T0	No primary tumour identified	No tumour seen
Tis	Carcinoma in situ (limited to mucosa)	1st hypoechoic layer is expanded but second hyperechoic layer is intact
T1	Tumour invades submucosa, but does not involve muscularis mucosa	No disruption of the bright middle hyperechoic layer
T2	Tumour invades muscularis propria	Tumour confined by the hypoechoic layer of the muscularis propria with no disruption of the bright interface between it and surrounding fat
T3	Tumour invades peri-rectal fat/ serosa	Outer hyperechoic layer disrupted, with the tumour edge usually irregular and has sawtooth projections
T4a	Tumour penetrates to the surface of the visceral peritoneum	The majority of rectal tumours cannot be staged due to the absence in the majority of a serosal surface
T4b	Tumour directly invades or is adherent to other organs or structures	Tumour extends into neighbouring organs

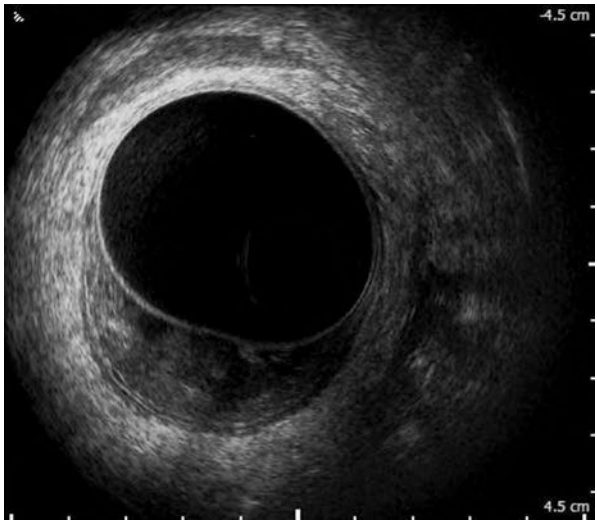

Fig. 2.2 An early rectal carcinoma uT1

TEM are being broadened when it is combined with neoadjuvant therapy. The TREC UK multicentre study addresses the current dogma that patients with T2 tumours are advised to have radical TEM surgery [22]. This trial will recruit early tumours randomizing the T1-2N0M0 cases to surgery or to short course preoperative RT with a delayed local excision.

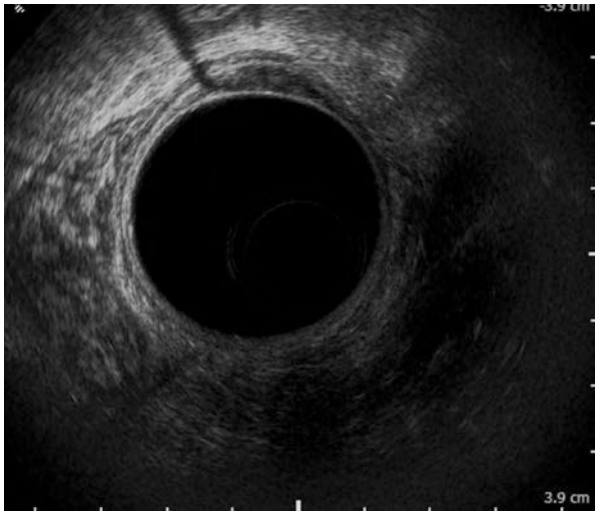

Fig. 2.3 An uT2 rectal carcinoma with disruption of the middle submucosal hyperechoic layer

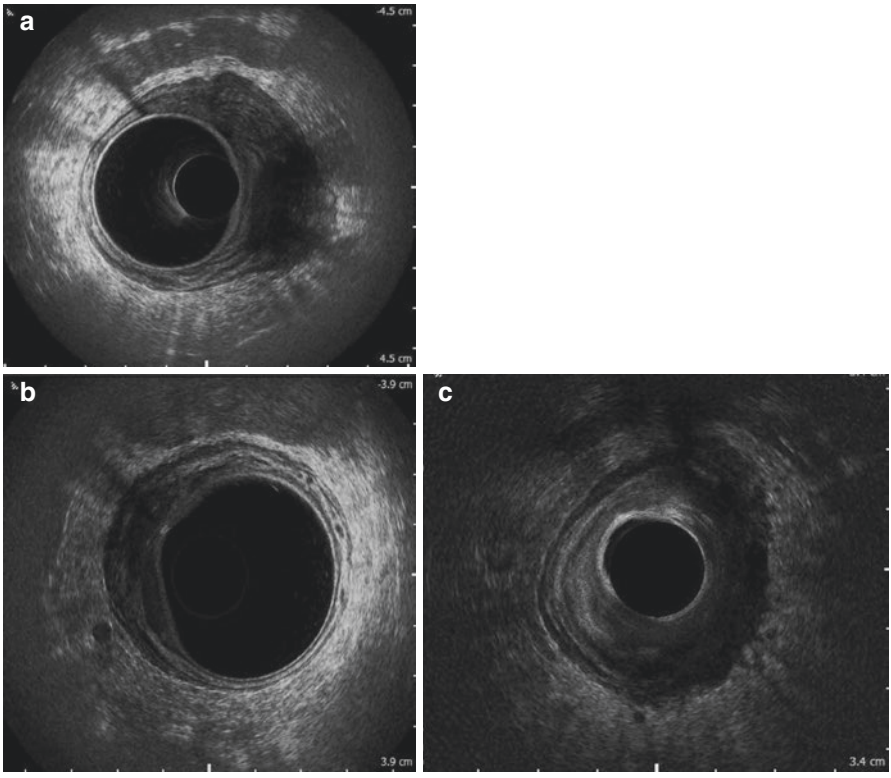

Fig. 2.4 An uT3 tumour with obvious saw tooth appearance of the tumour out into the peri rectal fat. (**a**) Example of uT3 tumour with obvious saw tooth appearance of the tumour out into the perirectal fat. (**b**) and (**c**) Examples of uT3 tumours with obvious saw tooth appearance of the tumour out into the perirectal fat with adjacent lymph nodes

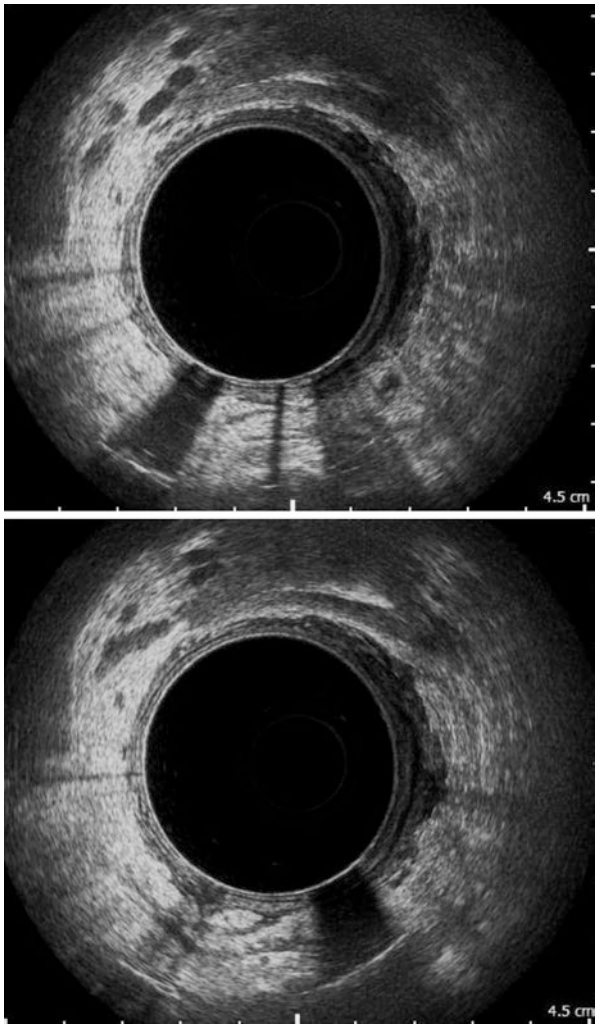

Fig. 2.5 An uT4 tumour with invasion into vagina confirmed histologically following resection

ERUS in Advanced Rectal Cancer

Most patients diagnosed with rectal cancer present with disease that has penetrated into or beyond the muscularis propria (>T2 disease). In this circumstance, patients may benefit from neoadjuvant radiotherapy or chemoradiotherapy (CRT), with the aim of downsizing and downstaging the more advanced primary lesion. This may allow modification of the subsequent surgical strategy where in selected cases the tumour may become suitable for an organ- and sphincter-preserving local excision rather than a formal TME or in some cases an Abdomino-Perineal Excision (APE) [22, 23]. In other circumstances some tumours deemed unresectable may become surgically

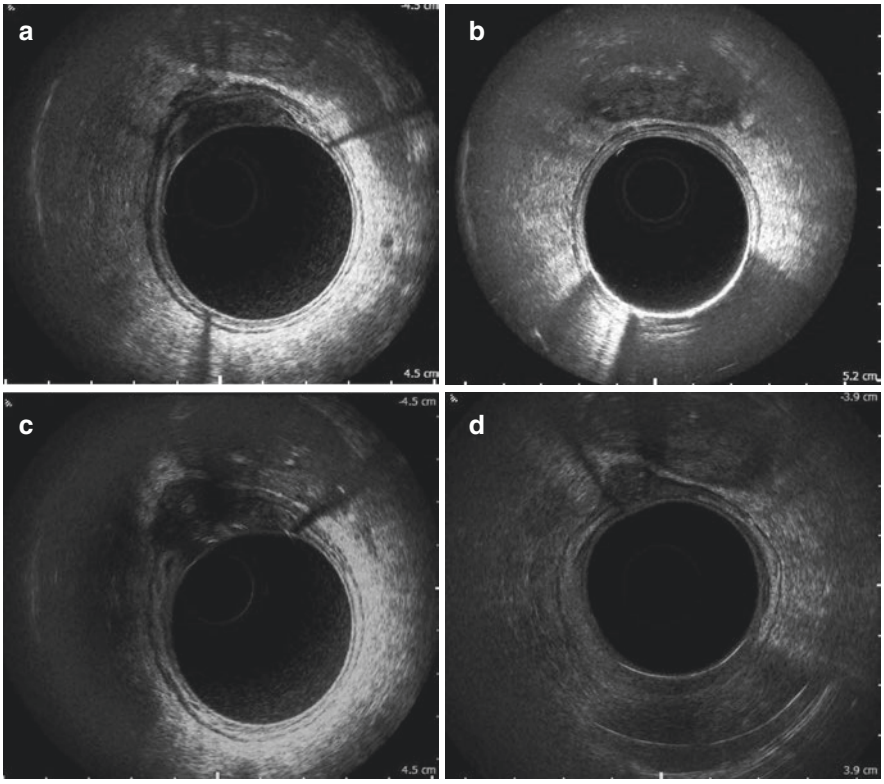

Fig. 2.6 (**a**) An uT4 tumour invading the prostate with peri rectal hypoechoic lymph node. The bright layer of Dennonvillier's fascia is clearly seen to be disrupted. This tumour was treated with long course chemoradiotherapy. (**b**) The same tumour after treatment with complete clinical, radiological and pathological response with now a normal ultrasonic appearance of the rectum and prostate. (**c**) Further anterior images confirm a sizeable recurrence clearly breaking the hyperechoic submucosa and re-infiltrating the fascia of Denonvilliaers just below the prostatic capsule. (**d**) The same tumour after careful clinical, endoscopic and radiological review now showing re-emergence of the tumour on the anterior rectal wall

resectable [24], with some low rectal tumours able to be downsized to such an extent that sphincter preserving surgery becomes feasible. Moreover, there are some patients who may achieve a complete response to CRT that has led some authors like Habr-Gama in particular to advocate a 'watch and wait policy' as opposed to immediate surgical resection [25]. The distinction between <T3 and ≥ T3 disease and those cases with T4 disease are clinically important decisions in order to identify patients who should be should be considered for neoadjuvant therapy and those in whom *en-bloc* multi-visceral resection should be used. In this respect, the roles of both ERUS and MRI in distinguishing between perirectal tissue invasion (T3) and adjacent organ involvement have been widely evaluated in the literature. The results of the 16 year meta-analysis of the literature comparing the modalities are presented in Table 2.2.

Table 2.2 Sensitivity and specificity summary estimates for endorectal US and MRI in the staging of rectal cancer

Stage	Imaging Modality	Sensitivity % (95% C.I.)	Specificity % (95% C.I)
Peri-rectal tissue invasion	ERUS	90% (88–92)	75% (69–81)
	MRI	82% (74–87)[a]	76% (65–84)
Adjacent organ invasion	ERUS	70% (62–77)	97% (96–98)
	MRI	74% (64–79)	96% (95–97)
Lymph node involvement	ERUS	67% (60–73)	78% (71–84)
	MRI	66% (54–76)	76% (59–87)

Adapted from Bipat et al. [19]
[a]Comparisons are significantly lower than ERUS

ERUS and Nodal Involvement

Lymph node metastases are one of the strongest predictors of survival and also of local failure in patients with rectal cancer. Consequently, if pre-operative staging investigations suggest lymphatic involvement the patient can be offered pre-operative CRT in the hope of sterilizing the nodal disease prior to surgical resection. The success of ERUS in predicting local invasion naturally led to its use to try and also predict lymph node metastases. Normal perirectal lymph nodes are not usually seen sonographically, however, abnormal malignant nodes can often be identified [26] (Figs. 2.4 and 2.6).

Sonographically malignant lymph nodes generally appear larger (>3 mm), and hypoechoic and non-homogenous as well as more circular in shape with well-defined borders when compared with non-involved nodes [26]. It should, however be noted that even with these discriminating features that radiological prediction (ERUS or MRI) of nodal involvement can be limited by the indistinct nature of the discriminatory characteristics. Lymph node size can be particularly unreliable in predicting metastatic involvement as small nodes can harbour small foci of disease, whilst large nodes can merely be inflammatory particularly when the ERUS is performed some time following biopsy of the rectal tumour mass [27]. Specifically concerning this point, Herrera-Ornelas et al. in colonic cancer noted that one-third of metastases may occur in lymph nodes less than 5 mm. in maximal diameter [28] with Dworák noting that one-third of metastatic disease within lymph nodes around rectal cancer was as a micrometastasis [29]. In both of these settings, standard imaging of lymph nodes will be negative limiting the overall sensitivity of the test.

The previously quoted 16 year meta-analysis of ERUS *vs* MRI in staging rectal cancer found that ERUS had a sensitivity of 67% and a specificity of 78% for lymphatic involvement whereas MRI had a sensitivity of 66% and a specificity of 76% (see Table 2.2) [19]. There are therefore significant limitations of both ERUS and MRI in the prediction of lymphatic involvement but at present these modalities represent the best available techniques. Concerning this point there was hope that

positive emission tomography (PET) scanning would be useful but it has emerged that PET-CT scanning cannot discriminate between the FDG-avid primary tumour and positive nodes which are situated in close proximity to the tumour [30].

Potential Pitfalls with ERUS

ERUS is undoubtedly useful in the staging of early and locally advanced rectal cancers alike. However, there are some limitations that require comment. The excellent results achieved in some units have not been mirrored in other departments where there are overall reported accuracies with wide ranges for ERUS varying from between 54% to 92% accuracy [31–33]. This discrepancy may arise in part due to the operator-dependent nature of the technique [34]. Further, publication bias may contribute to this disparity with an artificially high accuracy reported in the positive literature [35]. In most series where ERUS staging has been inaccurate, the trend is for patients to have been over- rather than under-staged [34, 36] with a more serious impact of under-staging on patient care as opposed to the overtreatment of the over-staged case and the tendency because of this towards overdiagnosis reporting.

Usually conventional 2D ERUS is unable to define the mesorectal plane, limiting its use when making decisions concerning CRM involvement and the potential neoadjuvant treatment, where MRI is considered to be the superior imaging and complementary modality. There has been recent interest that 3D ERUS may have a role in the assessment of involvement of the mesorectal plane but at the present time there is insufficient data to recommend addition of this technique [37]. Similarly, not all perirectal and IMA-related lymph nodes are within reach of the sonographic image signaling an advantage for MRI along with the ability to detect extrarectal metastatic disease.

ERUS is also of limited value in patients who have an obstructing tumour where luminal narrowing may preclude adequate deployment of the ERUS probe. ERUS may also be inaccurate in patients who have distorted anatomy secondary to a pre-ultrasound tissue biopsy where there may be coincident haematoma formation or following a polypectomy that has revealed a focus of malignancy requiring formal staging. Neoadjuvant chemoradiotherapy is also a significant problem when using ERUS as it can be difficult to differentiate between the usual post-CRT tissue reaction and ongoing malignant disease and where the typical individual rectal wall layers are not ultrasonographically discernable [38, 39].

ERUS after Neoadjuvant Chemo-Radiotherapy

Neoadjuvant chemoradiation (CRT) which is increasingly being used in rectal cancer management may result in selected patients with complete tumour resolution and in others with significant downstaging permitting local tumour excision [22–24, 40].

One of the challenges in these scenarios is to correctly identify those patients who can safely be managed in this way when CRT induces an inflammatory fibrotic reaction making the accuracy of endosonographic re-staging of the tumour a challenge. This can be particularly problematic when a 'watch and wait' policy is contemplated since fibrotic areas can harbour small foci of active disease that is impossible to distinguish from post-radiotherapy change.

It has been widely reported that the accuracy of local staging after CRT is reduced (with any of ERUS, MRI or CT) due to this difficulty distinguishing between inflammatory change in scar and viable malignant tissue. In a series of 46 patients with mid/low rectal cancer reported by Maretto and colleagues, ERUS was found to accurately predict T stage in 64% of patients and N stage in 61% of patients, a finding very similar to the accuracy on MR and CT [41]. Huh et al. examined comparative ERUS (n = 60) and CT (n = 80) staging post-CRT and found that the T stage was predicted accurately in 38% of patients with ERUS as against 46% with CT, and with N stage accurately predicted in 73% by ERUS and 70% by CT [42]. Of importance in this study was the finding that none of the 11 patients who experienced a complete response were identified as such by either modality. A further study of 44 patients by Radovanovic et al. [43] found ERUS predicted T stage accurately in 75% of patients with N stage accurately predicted in 68%. In this series there were five patients who had a complete pathological response to CRT but ERUS only predicted one of them. In a further study of 90 consecutive patients Pomerri et al. [44] found that all modalities had a poor accuracy for predicting T stage after CRT (ERUS 27%, MRI 34% and CT 37%). In this study, N stage accuracy was higher but was similar between the different imaging modalities (ERUS 65%, MRI 68% and CT 68%) where they reported that mural staging by ERUS was much improved if the T stages were stratified as ≤T3 and T4. With this categorization, the sensitivity and specificity were 92 and 95% respectively, however, it must be recognized that there were only seven patients with T4 disease in their analysis.

The relatively poor accuracy of post-CRT local staging is one of the biggest problems faced when trying to predict which patients have either had a complete response or which could potentially be treated by organ-preserving surgery with local excision of any foci of remaining tumour. At present, it is the therefore the authors own practice to base all post-treatment surgery on pre-CRT rather than post-CRT imaging results.

ERUS and the Detection of Local Recurrence

Despite improvements in the treatment and surgery for rectal cancer, local recurrence still occurs in some patients. If local recurrence is detected at an early stage it may be possible to resect the recurrence with the aim of long-term cure. The ability of ERUS to detect local recurrence before it becomes symptomatic has been evaluated in several small series [45, 46], which have reported that up to 25% of

asymptomatic local recurrences can be identified on ERUS before they become symptomatic. Because ERUS is relatively inexpensive and portable it could be included in a routine follow up protocol. In this setting, assessment of the neorectum is, in essence, no different to examination of the true rectum in that the typical layers can still be clearly identified. The presence of a stapled anastomosis also does not affect the interpretation of the images, where staples are seen as small bright echoes without any attendant acoustic shadowing.

Following surgery the ultrasonic anatomy of the pelvis may, however, alter and significant care is therefore required in the interpretation of the images obtained. Here, it is recommended that scanning is not performed until 3 months after surgery due to the confusion that a normally resolving post-operative appearance may cause. The endosonographic appearances of intra-luminal local recurrence are identical to those of primary rectal cancer and are echo-poor in nature. The extent of invasion of the recurrence can be assessed in a similar manner to primary rectal cancer. Extra-luminal recurrences will also appear as echo-poor circumscribed nodules in the para-anastomotic area. Given these ground rules there is also the caveat that a single ERUS examination alone may not be diagnostic for local recurrence as demonstrated in the case study of Figs. 2.6. In this situation one of two strategies can be employed; namely the performance of a repeat ultrasound after a delay of 4–6 weeks (where an increase in size will usually indicate recurrent malignancy), or use of the endoprobe to guide a biopsy of the area of concern [47]. This technique requires a specialized removal needle guide housing and can be performed either directly with an 8808 probe (B&K Medical Herlev Dk) and an automated biopsy needle (ASAP Automated Biopsy System, Boston Scientific, MA) or by a simpler direct visualization technique depending upon the precise location of the suspected recurrence. The former technique can be performed by a single operator with software calculation of the needle depth in real time.

Conclusions

Since the first use of ERUS to locally stage rectal cancer 30 years ago there have been radiological, surgical and oncological treatment advances that necessitate accurate pre-treatment T and N stage prediction in order to provide each individual patient with a bespoke tailored treatment that is optimal for their disease stage [48]. The advantages of one imaging methodology over another have reflected the limitations of its competitors in the assessment of the primary tumour and its draining nodal burden [49] as well as in the specialized determination of the degree of response to aggressive preoperative chemoradiation. Within the scientific literature there have been numerous publications that have attempted to answer the principal question as to whether which of ERUS or MRI is the more accurate modality. In reality both although competitive can be complementary to some extent with their own specific advantages and disadvantages with translatability worldwide [50].

Table 2.3 Comparison of the merits and disadvantages of ERUS and MRI in the management of rectal cancer

	ERUS	MRI
Identification of early mucosal disease	Superior	Inferior
Distinction between <T3 and>T3	Superior	Inferior
Adjacent organ invasion	Similar	Similar
Lymph node involvement	Inferior	Superior
Threatened CRM	Inferior	Superior

In this regard some of the physical acoustic aspects of endosonography will provide limits on this particular modality (Table 2.3). It is the authors' opinion that both techniques should be used in all cases of rectal cancer so as to optimize the staging and decision making concerning patient management.

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Chapter 3
The Role of MRI in Assessment of Rectal Cancers

Muhammed R. S. Siddiqui, Svetlana Balyansikova, and Gina Brown

Introduction

Magnetic resonance imaging (MRI) for rectal cancer staging has evolved to not only include T and N stage but also to identify poor prognostic features such as circumferential resection margin (CRM), MRI identified extra-mural vascular invasion (mrEMVI) and tumour regression (mrTRG) [1–8]. The detailed assessment of tumour characteristics has been facilitated by the development of more modern scanners and pelvic phased-array coils. These improvements have led to more accurate assessment resulting in appropriate selection of locally advanced tumours requiring neoadjuvant therapy and post treatment regression evaluation [1, 8]. The ability of MRI to assess features with greater detail enables risk-stratification and more effective patient-specific management particularly within the context of multidisciplinary treatment (MDT) meetings. This approach for the management of patients with rectal cancer patients is increasingly considered the gold-standard across all secondary and tertiary referral centers [9].

This chapter provides an overview of the clinical role of MRI in the staging of specific prognostic features present on imaging in patients with rectal cancer.

M. R. S. Siddiqui
Department of Colorectal Surgery, Croydon University Hospital, Croydon, Surrey, UK

Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, UK

S. Balyansikova · G. Brown (✉)
Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, UK
e-mail: Gina.Brown@rmh.nhs.uk

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MRI Technique

Rectal cancer staging using MRI scans depends upon high resolution imaging and systematic interpretation of the images. There are three main areas related to effective assessment that require consideration; these are appropriate patient counselling, correct coil position and appropriate imaging sequences. Originally endo-rectal coils were used to image rectal tumours and produced T2-weighted images of equivocal quality and staging was considered inaccurate [10, 11]. Endo-rectal coils had further drawbacks including the inability in some cases to deploy coils through narrow strictures and motion artefact [12]. These limitations were overcome by the development of pelvic phased-array coils which approach similar resolutions as the endorectal coils but did not have the disadvantages of rectal deployment. In general, the placement of coils is critical in ensuring appropriate image acquisition where for rectal tumours distal to the mid-rectum, the pubic symphysis functions as the center of the view. By contrast, more proximal tumours need a more rostral centering of the coil [13].

High resolution images may take up to 40 min to provide good-quality images used for staging purposes. In some patients, the length of the procedure may be challenging and they should be counselled prior to the MRI in order to avoid motion artifact, patient discomfort (e.g. need to pass urine) and in rare cases claustrophobia (in our experience typically less than <1%). In circumstances where perceived patient concerns are too great, sedation or sedative analgesics may help [14, 15].

High-resolution T2-weighted imaging sequences are considered the gold-standard as reported and validated by the MERCURY study group [3, 15]. The planning scan facilitates appropriate image capture in the oblique axial and oblique coronal planes, however, clinicians should ensure effective communication regarding the endoscopic tumour site as this will ensure better coil positioning especially in relation to the proximal (at least 5 cm) and the distal (at least 1 cm) borders. Slice thickness is usually 3 mm as opposed to 5 mm typically seen in standard MRI scans, so as to allow for higher definition imaging. This is of particular importance especially catering for angulated rectal anatomy which may require repositioning of the coils in the sagittal planes. The higher resolution also permits a more careful scrutiny of some prognostic factors such as mrEMVI [16].

MRI and Clinical T Stage

Primary tumour characteristics remain the most important determinants of prognosis and appropriate assessment relies on accurately determining tumour invasion. Tumour stage evaluation using MRI principally follows the histopathologic TNM classification [17] however, it is modified in accordance with radiologically defined criteria (Table 3.1) [4, 13]. In addition, morphological features may provide information regarding the most invasive area of the tumour. Tumour height may also be

Table 3.1 Tumour staging using MRI

Tx	Primary tumour can not be assessed
T0	No evidence of primary tumour
T1	Tumour invades submucosa (low signal in the submucosal layer; replacement of the submucosal layer by abnormal signal not extending into the muscular layer)
T2	Tumour invades but does not penetrate muscularis propria (intermediate signal intensity, which is higher than muscle but lower than submucosa, in the muscularis propria; outer muscle coat replaced by tumour of intermediate signal intensity that does not extend beyond outer rectal muscle into rectal fat)
T3	Tumour invades subserosa through muscularis propria (broad based bulge/nodular projection, not fine spiculation, of intermediate signal intensity projecting beyond outer muscle coat)
T3a	Tumour extends <1 mm beyond muscularis propria
T3b	Tumour extends 1–5 mm beyond muscularis propria
T3c	Tumour extends 5–15 mm beyond muscularis propria
T3d	Tumour extends >15 mm beyond muscularis propria
T4	Tumour invades other organs (extension of abnormal signal into adjacent organ (v) or extension of tumour signal through peritoneal reflection (p))

adequately assessed thus determining the type of surgery offered, recently highlighted in the MERCURY II study [18]. Historically, MRI scans were able to effectively identify T1 and T2 tumours as a single cohort. It was felt that prognostically, T1 and T2 tumours shared similar long-term outcomes with 5-year local recurrence rates ranging from between 9–16% and with a 5-year overall survival of approximately 80% [19–21]. In these original series, the inability to distinguish between T1 and T2 was not considered important because the management was the same. Due to improvements in local excision techniques the ability to identify tumours confined to the rectal wall has gained greater clinical importance since they can now be treated with less radical surgery. Recently MRI has been shown to predict partial invasion vs full invasion of the submucosa with 89% accuracy [22]. This may be in part due to the identification of a hyper-intense stripe between the tumour and muscularis on MRI scans and may be interpreted as preservation of the submucosal layer and hence represents a likely T1sm1/2 at most [23]. Lack of high-resolution imaging and necessary clinical experience in some centers means that this subdivision may preclude appropriate case selection in patients particularly where lesions are amenable to local excision. Therefore prospective trials are currently underway to validate MRI assessment of early rectal cancers [24–26].

Historically, the sensitivity and specificity of MRI for staging has been limited to the identification of T3 and T4 disease was 97% for T3 and T4 disease [27] However T3 disease forms a large and heterogeneous prognostic category and comprises more than 80% of rectal cancers.

The degree of invasion beyond the muscularis propria ranges from a spread of 1 mm (with identical prognosis to T2 tumours) to as much as >15 mm where the prognosis is so poor that about 75% of patients do not survive beyond 5 years. It is

therefore clinically relevant to sub divide the T3 group according to the original pathologic categories described by Hermanek into T3ab (<5 mm beyond the muscularis propria) and T3cd (>5 mm beyond the muscularis propria) [28]. Its prognostic relevance has been validated in multiple histopathology studies. The MERCURY study group compared the depth of spread measured by MRI versus depth of spread on histology and showed equivalence therefore the same prognostic stratification can be applied using the MRI depth of spread [29]. It is therefore recommended that instead of stating a tumour is staged as T3, subclassification into T3a(<1 mm)/b(1–5 mm) or T3c(5–15 mm)/d(>15 mm) is more useful [28]. Dividing T3 tumours into those with ≥ or <5 mm of invasion beyond the muscularis propria on histopathologic specimens has been examined in 13 trials and a subsequent meta-analysis of these studies [30–42] has suggested that overall survival (HR = 0.71), disease-free survival (HR = 0.67) and cancer-specific survival (HR = 0.82) is better in the less invasive T3 tumours (<5 mm) when compared with the more invasive tumour cohort [43]. This finding is of particular relevance during the pre-operative assessment using MRI to define the level of invasion. In a study of patients in our center, we found that those with less invasive tumours (T3a/b) on their baseline MRI were 3.5 times more likely to survive by 4 years of follow-up when compared with those with more invasive tumours [44]. In these cases, the muscularis propria on T2-weighted images is often visible as two separate discrete layers (the inner circular and the outer longitudinal) where the outer wall is frequently evident as irregular resultant from vessel perforations. This region is seen clearly as a low signal layer surrounded by a higher signal region representing the perirectal fat. Surrounding this area is the low signal mesorectal fascia defining the surgical total mesorectal excision plane [45].

The challenge of MRI assessment is to ensure high quality, high-resolution imaging and this may consequently explain the lower reported sensitivities in some of the older studies using less powerful imaging technology. Concerning this point, an earlier meta-analysis showed during a meta-regressional analysis that higher sensitivities and specificities were achieved using 3 T as opposed to 1.5 T machinery [46] highlighting the need to focus on high quality individual studies such as the MERCURY study. This latter group has reported that extramural depth (EMD) invasion of tumour spread was available in 95% of the patients (n = 311) where comparisons could be made with resection histopathology where the mean differences in the EMD values were minimal (−0.05 mm ± 3.85; 95% CI −0.49 to +0.40 mm) [29].

Overall MRI staging would be the modality of choice to stage rectal cancers to adequately stratify T-stages into good and poorer prognosis tumours.

MRI and Clinical N Stage

Despite an absence of any proven clinical importance in the TME era, pre-operative treatment of rectal cancer patients in many centers still relies on imaging of nodal status. Imaging assessment of nodal status has historically been based on size

criteria to differentiate between malignant and benign nodes however the authors believe have shown that the measurement of lymph node size results in inaccuracy and should not be relied on [47]. Furthermore histopathology studies suggest that there is no correlation between the nodal size and the biology of the changes developed [48, 49]. Metastases are quite often observed in nodes less than 3 mm and on the contrary hyperplastic benign nodes usually enlarged in size. MRI has been proven to be a reliable method of assessing visible nodes when morphological criteria such as nodal margins (irregular borders) and specific signal characteristics (heterogeneous signal intensity) are applied [4, 47]. The number of lymph nodes has also been previously considered a poor prognostic feature [50, 51] however, this may not be as relevant since the advent of total mesorectal excision which resects the affected lymph node bearing field *en bloc* within the mesorectal fascia as a lympho-vascular package [52, 53]. For staging purposes less than 4 suspicious nodes is considered N1 disease and greater than 4 nodes as N2 disease [17]. In this respect, there has been some debate regarding the role of lymph node yield in patients undergoing preoperative radiotherapy with some recent studies highlighting a clearly lower yield [54] and in the context of presumed sterilized lymph nodes, no difference in prognosis [55]. Rather than focusing upon the number of nodes it may be more appropriate to consider extra nodal tumour deposits (n1c disease) as this highlights a worse prognosis. These extra-nodal deposits have been proven to be associated with mrEMVI resulting in a higher rate of developing metastatic disease than patients with mrEMVI negative but lymph node positive disease [56, 57].

Vascular invasion is considered a more important mechanism for lateral side wall spread [58]. Although traditionally seen as potentially important when close to the circumferential resection margin [59, 60], more recent work has shown that malignant lymph nodes rarely threaten the CRM on final histopathology specimens [61]. Development is still required in order to accurately classify tumour deposits on MRI scans in particular where a node looks suspicious and is in close proximity to the CRM. These tumour deposits (TD) would classically be reported as N1c disease however when these deposits are in proximity to a vessel, they may be more appropriately described as venous deposits rather than a node or separate entities altogether (from both mrEMVI and nodes) [56, 57, 62]. Furthermore, EMVI has the capacity to permeate beyond the mesorectal fascial envelopes unlike lymph nodes which harbour discrete tumour within encapsulated boundaries. This may explain why EMVI but not lymph nodes is an independent risk factor for CRM involvement and local recurrence after TME surgery [18, 63].

MRI and mrEMVI Status

The true prevalence of extramural vascular invasion (EMVI) has been historically debated. This is largely due to lack of standardised definitions reflecting the wide range of reported histopathological rates of 9–61% [5]. mrEMVI has a standardised definition and is described as a serpiginous extension of tumour signal within a vascular structure – resulting in contiguous or discontinuous expansion of a vein by

tumour signal [64, 65]. mrEMVI has been identified in 20–57% of cases and highlights the significant burden that this poor prognostic factor poses [66].

Extra-mural vascular invasion has been posited as the main route via which micro-metastases disseminate through the body [57, 66], rather than by the lymph node status/lymphatic spread and has attracted significant investigation due to its identification during the MRI staging process. In this regard, mrEMVI has been shown to have a five-fold increased rate of synchronous metastases and almost a four-fold ongoing risk for the development of metastases during the follow-up after surgery [16, 64, 67–70]. There is a need therefore to identify treatment strategies which improve the cancer-specific prognosis in this group of patients.

MRI and the Circumferential Resection Margin

The importance of the CRM was originally identified in 1986 where 86% of patients with CRM involvement after surgery went on to develop loco-regional recurrence [71]. The mesorectal fascia assumes special significance in the context of total mesorectal excision, through which local recurrence was found to be significantly lower when compared with historical non-TME extirpative surgery [72]. Where the CRM is involved during TME, the recurrence rates are still higher and in this context the CRM acts as an independent risk factor both for loco-regional recurrence and for overall survival [59, 72–75]. By accurately predicting the involvement of the CRM preoperatively on MRI, the surgical management may be tailored accordingly. On MRI, the mesorectal fascial envelope appears as a lower signal line encompassing the mesorectal fat, lymph nodes and lymphatics and the small vessels [75] and correlates to the fascial layer seen on histopathology specimens [76]. Using MRI, the mesorectal fascia and CRM may be differentiated from the adjacent structures such as Denonvilliers fascia and presacral fascia [45]. A positive CRM may typically be defined as proximity to the primary tumour or visible mrEMVI within 1 mm of the fascial edge [4, 77]. MRI is a good diagnostic modality for assessment of CRM involvement where a diagnostic meta-analysis has reported a sensitivity and specificity reaching 94% and 85%, respectively [78]. In this regard, some studies have used different cut-offs for histopathological diagnosis such as a size ≥2 mm despite using an MRI cut-off of 1 mm, a feature which may explain lower reported specificities [79]. Taylor et al. [80] had compared local recurrence rates using different definitions of CRM involvement that included a 1, 2 and 5 mm cut-off, in this analysis that was conducted by the MERCURY group only the 1 mm cut-off was predictive for local recurrence. Other reports have corroborated these findings, identifying the CRM status correctly in 98% of cases in a diagnostic meta-analysis by Zhang et al. [27]. Follow-up of the MERCURY study has confirmed the prognostic significance of the CRM as identified by MRI with a 5-year overall survival of 62.2% in patients with a clear CRM identified on MRI versus 42.2% in patients with a threatened or involved MRI-detected CRM [81]. An example of a low T3 tumour

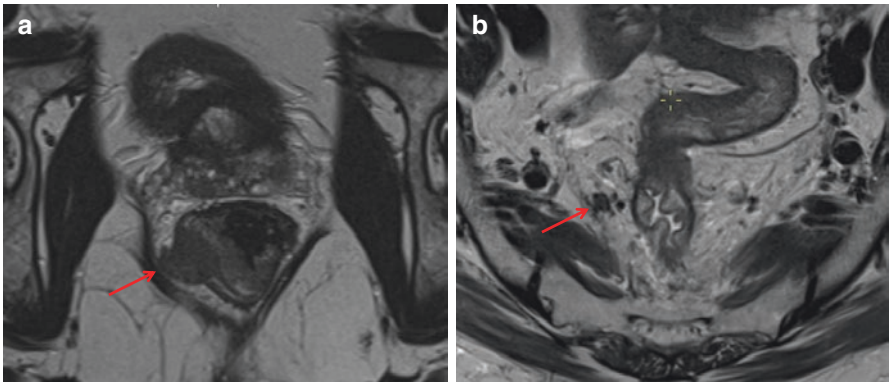

Fig. 3.1 (**a**) An mrT3d low rectal tumour infiltrating the rectal wall at 8–10 o'clock with evidence of spread beyond the muscularis propria. At 8–9 o'clock the primary tumour abuts the mesorectal fascia (arrow) and the right levator indicating that distance to CRM is <1 mm (CRM+ve). (**b**) A discontiguous vascular deposit/extramural EMVI at the 9 o'clock position (arrow) involving the mesorectal fascia suggesting CRM positivity

abutting the edge of the mesorectal fascia (CRM positive) with discontinuous EMVI is shown in Fig. 3.1.

Assessment of the CRM in T4 disease is even more relevant since the current classification is broadly divided into T4-peritoneal and T4-visceral. Diagnosis of invasion of the peritoneum can be challenging and an appropriate knowledge of anatomy is required [4]. What is more relevant is the involvement of compartments beyond the mesorectal fascia and in particular when considering surgery beyond TME. The beyond TME guidelines have recommended that compartments be fully assessed using high resolution MRI [82]. This was based upon the classification of tumour invasion into compartments which is potentially useful from both a surgical and prognostic perspective, where 2 or more compartment involvement (or singular if lateral/posterior) have a worse DFS [83, 84]. These compartments are defined and shown in Table 3.2.

MRI Assessment of the Response to Neoadjuvant Therapy

Locally advanced rectal tumours are often treated primarily with neo-adjuvant chemo-radiotherapy in an effort to reduce loco-regional recurrence [85]. It is now accepted that the degree of primary tumour regression following neo-adjuvant therapy, (as identified on the final histopathological specimens), is a prognostic factor [86]. The variation in response allows clinicians to risk-stratify patients following surgery, a process which may help in post-operative decision-making in when to treat with adjuvant chemotherapy and to decide about the intensity of follow-up.

Table 3.2 Classification of compartments for beyond TME surgery

	MRI; planes of dissection	C	Rectum or neorectum, intraluminal recurrence, perirectal fat or mesorectum, extraluminal recurrence	MRI diagnosis of tumour invasion within the lateral, posterior or in more than two compartments associated with reduced disease-free survival
		PR	Rectovesical pouch or rectouterine pouch of Douglas	
		AA PR	Ureters and iliac vessels above the peritoneal reflection, sigmoid colon, small bowel and lateral side wall fascia	
		AB PR	Genitourinary system	
		L	Ureters, external and internal iliac vessels, lateral pelvic lymph nodes, sciatic nerve, sciatic notch, S1 and S2 nerve roots, piriformis or obturator internus muscle	
		P	Coccyx, presacral fascia, retrosacral space, sacrum up to the upper level of S1	
		I	Levator ani muscles, external sphincter complex, perineal scar (APER), ischioanal fossa	

C central, *PR* peritoneal reflection, *AA* anterior above, *AB* anterior below, *L* lateral, *P* posterior, *I* inferior

The challenge, however, is how to utilize and standardize this information in order to alter the clinical course of post-operative recurrence and survival. There are currently 19 histopathology tumour regression (TRG) scales available, each of which are used in different combinations so as to produce a definition of good and poor response [87–106]. This challenge has been highlighted by MacGregor et al. who stressed the need for and importance of a universally accepted standard [107].

The MRI tumour regression grading system (mrTRG), which has been validated as a prognostic tool and has the additional advantage of being utilized prior to operative intervention has been designed to obviate these problems and has been shown to be both reproducible and readily teachable in a workshop setting (Table 3.3) [108]. A poor response on MRI (mrTRG 4 or 5) has resulted in a 5-year locoregional recurrence rate (LRR) between 4% and 29%, a distant recurrence rate (DRR) of 9%, a disease-free survival (DFS) between 31% and 59% and an overall survival (OS) of 27–68%. By contrast, the 5-year outcomes of patients with a discernably good response on MRI (mrTRG 1, 2 & 3) demonstrated a LRR of 1–14%, a DRR of 3%, a DFS of 64–83% and an OS of 72–90% [1, 7, 8, 109, 110]. Figure 3.2 shows an example of a low rectal tumour with contiguous EMVI and CRM+ve involvement of the mesorectal fascia with a good response to chemoradiation (low signal fibrosis only downgrading the EMVI and CRM stage). The use of mrTRG in routine practice may potentially enable a response-orientated tailored treatment which includes the possibility for sphincter preservation, the additional use of che-

Table 3.3 MRI tumour regression grading

mrTRG scale	mrTRG [Low no. – More regression]
1	Radiological complete response (rCR): no evidence of ever treated tumour
2	Good response (dense fibrosis; no obvious residual tumour, signifying minimal residual disease or no tumour)
3	Moderate response (50% fibrosis or mucin, and visible intermediate signal)
4	Slight response (little areas of fibrosis or mucin but mostly tumour)
5	No response (intermediate signal intensity, same appearances as original tumour)

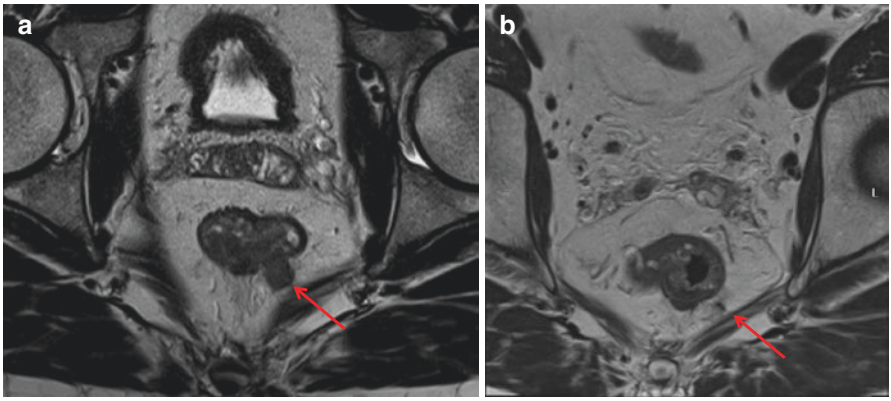

Fig. 3.2 (**a**) Baseline MRI showing a low/mid rectal tumour involving the rectal wall at 4–7 o'clock with evidence of spread beyond the muscularis propria (arrow). A contiguous EMVI of the mid rectal vein at 5 o'clock position extends up the mesorectal fascia suggesting CRM+ve disease (overall mrT3dN1cEMVI+ve CRM+ve). (**b**) The same patient post CRT MRI. Tumour shows good response to treatment (arrow) with only linear fibrosis identified at the site of the treated disease and an area of low signal/fibrosis at the site of the contiguous EMVI (5 o'clock position), (overall Stage mrT2N0EMVI-ve CRM-ve TRG2 if any viable tumour left)

motherapeutic cycles or in selected cases a more localised approach to resection. In addition to the overall tumour regression, sub-classification of T3 tumours into those which have >5 mm of infiltration after neoadjuvant chemoradiotherapy indicates a worse overall survival [111]. Further validation work is required in this area to ensure that these results are reproducible as this will have important implications for the scheduling of radiotherapy delivery. Figure 3.3 shows an example of a locally advanced low rectal tumour with EMVI with some response to neoadjuvant therapy but with a persistent intermediate signal suggestive of residual disease.

In addition MRI regression assessment of the EMVI status has been initiated with an mrEMVI regression grading system (mr-vTRG) (Table 3.4) and can effectively be divided into good and poor response cohorts [16, 65, 112]. In this schema, the response pattern is prognostically discriminatory with good responders (mr-vTRG 1–3) having a 3-year DFS of 87.8% and a 9% recurrence rate whereas poor responders (mr-vTRG 4–5) have a 3-year DFS of 45.8% and a 44% recurrence rate [65].

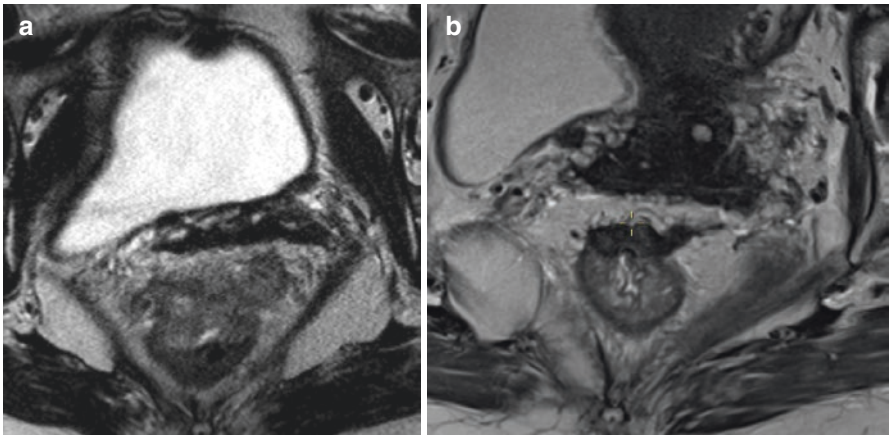

Fig. 3.3 (**a**) A pretreatment MRI demonstrates a locally advanced T3d low rectal tumour which infiltrates the rectal wall at 11–2 o'clock with evidence of contiguous EMVI involving the middle rectal veins. (**b**) A post CRT MRI of the same patient shows evidence of fibrotic changes within the treated scan, however the intermediate signal predominates within the intra and extraluminal components suggesting residual disease – TRG4

Table 3.4 mrEMVI regression grading (mr-vTRG)

mr-vTRG scale	mr-vTRG [Low no. – More regression]
1	Tumour signal replaced by vessel fibrosis
2	50–75% fibrosis of tumour signal
3	25–49% fibrosis of tumour signal
4	Less than 25% fibrosis of tumour signal
5	Minimal fibrosis of tumour signal within lumen

Summary

High resolution magnetic resonance imaging offers detailed analysis of rectal tumours during the staging process. It is able to accurately assess overall tumour stage and can differentiate between T1sm1/2 and T1sm3/early T2 tumours as well as sub-classify T3 lesions into T3a/b (<5 mm beyond the muscularis propria) and T3c/d (>5 mm beyond the muscularis propria). High resolution MRI facilitates accurate nodal assessment in respect to signal heterogeneity and differentiation of lymph nodes with vascular deposits associated with extramural vascular invasion (EMVI). It is highly accurate in identifying involvement of the circumferential resection margin with sensitivities over 90% allowing more appropriate case selection for beyond-TME surgery. MRI identified EMVI (mrEMVI) as an independent prognostic factor is readily recognised and has an important role in neoadjuvant treatment decisions. The current role of MRI has been developed to incorporate post-neoadjuvant therapy assessment and can effectively predict the degree of regression which is, in itself an independent prognostic indicator. This allows for patient-specific therapy and follow-up protocols.

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Chapter 4
Role of FDG PET-CT in Colorectal Cancer

Rohit Kochhar and Prakash Manoharan

Introduction

Colorectal cancer represents the second most common malignancy worldwide, with nearly one million newly diagnosed colorectal cancers each year or nearly 9% of all new cancer cases diagnosed [1, 2]. It is the fourth leading cause of cancer mortality worldwide and the second most common cause of cancer death in the United States amongst cancers which affect both men and women [3, 4]. Rectal cancer comprises over one-third of cases of all colorectal cancers and whilst colonoscopy and biopsy remain the gold standard modality for the initial diagnosis, imaging is vital with regard to the local staging and the identification of distant metastatic disease. As a whole-body imaging technique, fluorodeoxyglucose (FDG) positron emission tomography (PET) and PET-CT (computed tomography) have the unique capability of providing local staging for the tumour and distant metastatic disease assessment in a single imaging session. This chapter covers the role of FDG PET-CT for diagnosis, initial staging (local and metastatic disease), re-staging and response assessment in patients with colorectal cancer with particular emphasis on rectal cancer. A summary of key learning points is given in Table 4.1.

R. Kochhar (✉) · P. Manoharan
The Christie NHS Foundation Trust, Manchester, UK

University of Manchester, Manchester, UK
e-mail: Rohit.Kochhar@christie.nhs.uk

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Table 4.1 Key learning points of FDG PET-CT imaging in colorectal cancers

1.	Knowledge of the patterns of physiological FDG uptake in the large bowel and artefactual uptake secondary to drugs such as metformin is important to avoid false positive results.
2.	Current guidelines do not recommend the use of FDG PET-CT for initial diagnosis and routine staging of colorectal cancer.
3.	The main role of FDG PET-CT in restaging patients with potentially resectable metastatic disease is to avoid futile surgeries by identifying unexpected extrahepatic disease not seen on conventional CT or MR imaging.
4.	If hepatic resection is planned then dedicated contrast enhanced MRI should be performed in addition to FDG PET-CT for all patients with potentially resectable hepatic metastases as a prerequisite, preoperative assessment tool.
5.	FDG PET-CT is now the initial test of choice for evaluating patients with a suspicion of local recurrence because of its high accuracy in lesion characterization.
6.	FDG PET-CT is a useful problem solving test for evaluating patients with rising tumour markers and a negative conventional diagnostic work up.
7.	FDG PET-CT post CRT can identify functional tumour response but fails to accurately predict the pathological complete responders.
8.	False negative FDG PET-CT results can be seen due to the small size of the lesion (<6 mm), mucinous nature of the primary disease and assessment done soon after neoadjuvant chemotherapy (<4 weeks). In addition PET-CT performed too soon after surgery (within 6 weeks) or radiotherapy (within 8 weeks) may be false positive due to inflammatory uptake.

Positron Emission Tomography (PET)

Technique

PET is a nuclear medicine examination utilizing 18F-fluoro-2-deoxy-D-glucose (FDG) as a primary tracer. The FDG-PET component provides metabolic information by utilizing the intensity of FDG uptake as a surrogate measure of a tumour's metabolic activity and this uptake can be assessed both qualitatively (via visual examination of the degree of uptake of a tumour relative to the blood pool) and quantitatively (via a standard uptake value - SUV value). Not only is FDG taken up by tumours, but there is also some degree of physiologic uptake by normal tissues and organs including a physiological bowel uptake and an artefactual bowel uptake which can be seen in response to administered medications (Fig. 4.1). Careful evaluation of the spectrum of uptake pattern is mandatory in order to avoid false-positive interpretations.

PET is now almost always performed in conjunction with a CT in dedicated hybrid PET-CT scanners. CT provides attenuation correction data and acts as the anatomic reference frame of the hybrid imaging [5]. This is performed either as a non-diagnostic, non-contrast CT intended only for accurate localization of lesions or abnormalities seen on the PET portion of the study, or alternatively, as a dedicated diagnostic quality intravenous iodinated contrast-enhanced CT meant to serve as both a localizer and as a stand-alone, diagnostic-quality multi-detector CT examination [6]. The routine use of bowel preparation and oral contrast for PET–CT in

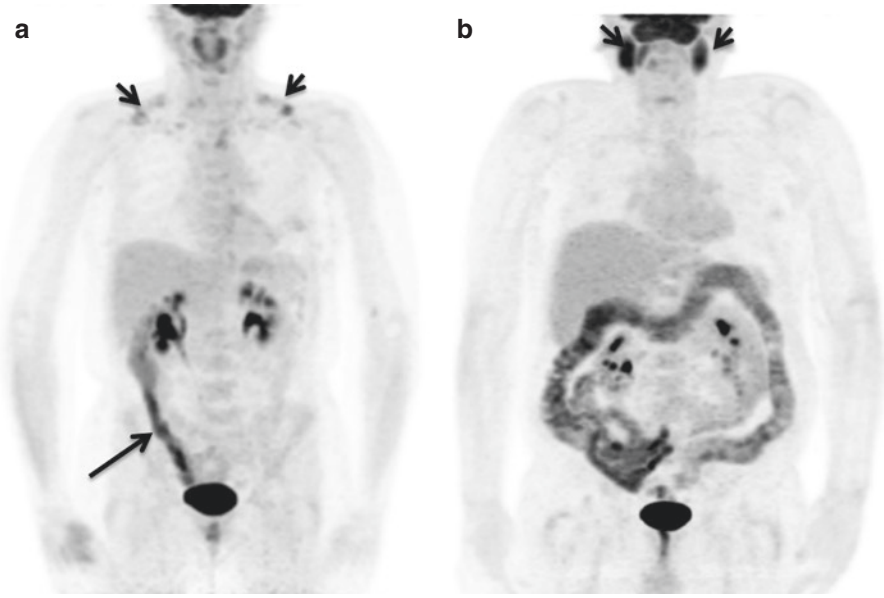

Fig. 4.1 Spectrum of bowel uptake on FDG PET-CT. MIP (maximum intensity projection) images of FDG PET-CT in two patients. (**a**) is showing *physiological bowel uptake* which can be seen in the right colon and usually this uptake is of low to intermediate intensity, homogeneous, and linear with no corresponding abnormality on the CT component of the study. Physiological uptake in brown fat is also noted in the neck (arrows in **a**). (**b**) showing diffuse increased FDG uptake in the large bowel predominantly right colon and to lesser extent in the small bowel. This is in keeping with artefactual metformin induced bowel uptake which limits the sensitivity of FDG PET-CT in assessing bowel pathology

colorectal cancer is debatable. Liquid low-density oral contrast agents (a mixture of locust bean gum and mannitol) have a lesser degree of intestinal uptake when compared with positive contrast agents and are favourable in their use for PET-CT. This type of contrast agent is commercially available in the United States but not in Europe. Potable water can be used as a simple and highly cost-effective negative oral contrast agent. From a technical point of view, intravenous as well as oral contrast-enhanced CT can be used for attenuation correction in PET-CT imaging without degradation of PET images in the abdomen, however in the majority of cases, the CT component is conducted as a non-contrast CT.

Patient preparation is vital and consists of fasting for 6 h prior to the FDG PET-CT scan. Patients are scanned from the skull base to the proximal thighs using a dedicated PET-CT scanner and the clinical standard in many centres is to image 60 min following injection of approximately 350 MBq of 18FDG or 5 MBq/Kg with capillary glycaemia measurement (less than 2.0 g/L). On the basis of the SUV max, lesions can be classified as having low (SUV max < 2.5), intermediate

(SUV max 2.5–5) or high intensity uptake (SUV max > 5). This semi-quantitative analysis is partly dependant upon the underlying metabolic status of the individual and therefore as a reference the circulating blood pool activity and liver activity is worth noting as a background. Examples on how this semi-quantitative assessment can be utilized are dependent upon the overall status of the area/lesion of concern. Focal intermediate to high intensity FDG uptake with a corresponding lesion on the CT component (for example a lung or an hepatic lesion) is taken to represent a metastasis. To compensate for the limited intrinsic resolution of PET (5–7 mm), enlarging or new focal lung lesions are considered metastatic regardless of their SUV. Anatomically stable lesions over a period of time demonstrating low intensity uptake below the blood pool/background activity can on the whole be regarded as benign.

Indications of FDG PET-CT in Colorectal Cancer

The current evidence-based indications for the use of PET-CT in the UK in colorectal cancers are summarized below [7].

1. Staging of patients with synchronous metastases at presentation suitable for resection or patients with equivocal findings on other imaging; for example, pulmonary or liver lesions.
2. Restaging of patients with recurrence being considered for radical surgery and/or metastasectomy.
3. Detection of recurrence in patients with rising tumour markers and/or clinical suspicion of recurrence with normal or equivocal findings on other imaging.
4. Evaluation of indeterminate pre-sacral masses post-treatment.

FDG PET-CT for Diagnosing and Local Staging of Colorectal Carcinoma

Based upon the available evidence, the use of FDG PET-CT in the initial diagnosis of colorectal cancer is not justified [8]. Non-enhanced FDG-PET-CT [9, 10] and contrast-enhanced PET-CT [11, 12] have gained a progressively important role in the evaluation of distant nodal (N), metastatic (M) staging and follow-up of colorectal cancer, however, the performance of PET-CT in the evaluation of the primary tumour (T) parameter has not been extensively investigated.

Accurate T-staging is not possible with PET-CT as it does not provide the anatomic detail or the spatial resolution to accurately judge the degree to which a tumour extends through the rectal wall [13]. The sensitivity for detection of locoregional nodal metastases is also low because lymph nodes are usually close to the primary tumour and cannot be differentiated from it as a result of ‘blooming’ (high

intensity radiotracer uptake in the primary lesion which artefactually extends into the adjacent soft tissues and obscures the uptake in small mesorectal nodes) [14]. In addition many of these mesorectal nodes measure 5 mm or less which is below the spatial resolution of PET (Fig. 4.2).

A study using combined PET-CT colonography with dedicated colon preparation and image-acquisition protocols reported that in staging colon cancer, combined PET-CT colonography delivers accuracies which are superior to either CT

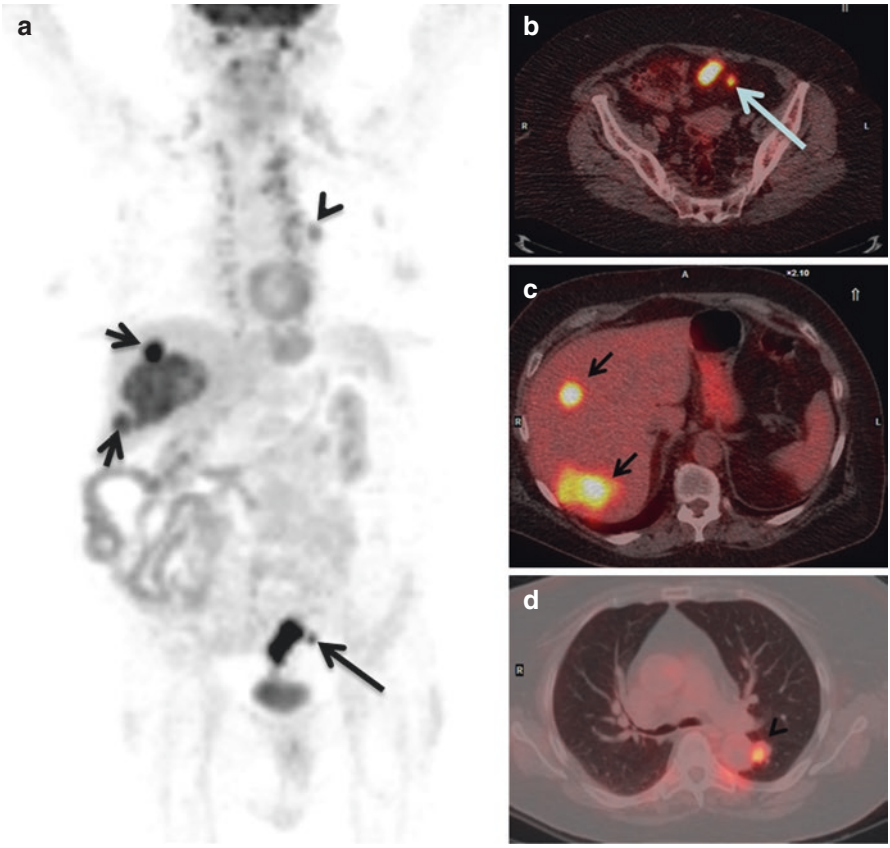

Fig. 4.2 Staging of colorectal cancer on FDG PET-CT. 86-year-old female with rectal bleeding due to a primary sigmoid cancer confirmed on colonoscopy. FDG PET-CT MIP image (**a**) demonstrating high intensity FDG uptake in the sigmoid lesion and in a small adjacent pericolonic node (long arrow). Staging MR had shown several adjacent pericolonic nodes however these are below PET-CT resolution and were partly obscured by the bloom associated with the intense uptake in the primary. Axial fused images of the same patient showing the intense uptake in the sigmoid tumour and adjacent node (long arrow in **b**), multiple FDG avid hepatic metastases are also clearly seen (short arrows in **c**) and a FDG avid pulmonary metastasis is also noted (arrow head in **d**). PET-CT has the unique ability of providing complete staging information as a single hybrid modality

alone and to CT plus PET performed separately [15]. However, the PET-CT colonography protocol is comparatively costly and may not be tolerated well by some patients. Moreover, it can be time consuming and it is not recommended in patients with impaired renal function. As such, PET-CT is not presently part of the international guidelines for initial staging of colorectal cancers [8, 16]. Its use is, however, recommended when CT is inconclusive or equivocal in advanced colorectal cancer cases [17]. Studies focussing specifically on rectal cancer have shown a significant percentage (around 30%) change of tumour stage with FDG PET [18] and a change in treatment plan on PET-CT [19] which is more frequent in low rectal cancers (27%) in particular, principally after the detection of positive inguinal lymph nodes [10]. Rectal cancer staging raises the specific questions of tumour volume delineation for radiotherapy treatment planning and of the monitoring of tumour response to preoperative chemoradiation which is the standard of care for locally advanced tumours. These issues are discussed in more detail below.

18F-FDG PET-CT in Management of Colorectal Cancer Patients with Metastatic Disease

About 20% of patients with colorectal cancer are diagnosed with metastatic disease at their initial presentation with the liver, lungs and peritoneum being the most common metastatic sites [20]. With modern surgical techniques and advanced chemotherapy, there is an important and increasing subset of patients with metastatic colorectal cancer who are considered for treatment with curative intent. Even if multiple metastases are present, surgical resection can result in long-term survival of between 35% and 58% of selected patients [21]. Accurate restaging of patients with potentially resectable metastases is therefore crucial for optimal management and 18F-FDG PET-CT has an increasingly important role in this setting [8, 22].

Conventional imaging with CT often fails to preoperatively identify those patients whose metastases can be successfully resected (Fig. 4.3). About 15–25% of cases are deemed unresectable at the time of surgery where disease recurs within 3 years in 60% of patients so classified [8]. Several studies have shown the impact of PET and/or PET-CT on the management of this subgroup of patients. In a study of 157 patients with colorectal cancer with potentially resectable liver and/or pulmonary metastases our group compared the findings on PET-CT with conventional imaging and the overall impact on patient management was assessed [23]. PET-CT upstaged disease in 33% of cases, downstaged disease in 24% and was in agreement with conventional imaging in the remaining 42% of patients. Based upon the PET-CT results in this study, surgery was averted in 34% of patients. A study by Scott et al. reported detection of additional lesions in 44% with a change in the management plan in 49% of patients [24]. A survey of physicians who referred patients with colorectal cancer for PET found that the PET findings contributed to a management change in 62% of patients [25]. In another similar study by Kong et al.

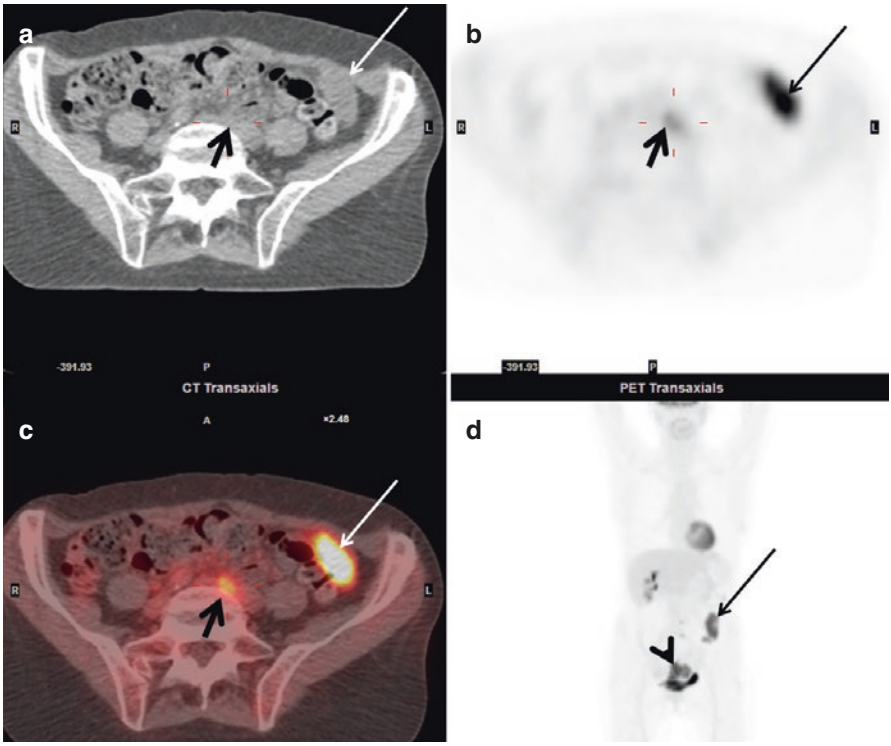

Fig. 4.3 Detection of unsuspected metastatic disease with FDG PET-CT. 69-year-old female with rectosigmoid cancer. Conventional imaging revealed a rectosigmoid carcinoma with solitary left omental deposit. On FDG PET-CT the omental deposit (long arrows) and the rectosigmoid primary (arrow head on MIP image **d**) both demonstrated high intensity FDG uptake. However in addition a left para-aortic node also demonstrated high intensity uptake (thick short black arrows) highly suspicious for metastatic retroperitoneal nodal disease making the patient unsuitable for curative surgery

[26] in 65 patients with colorectal cancer and known or suspicious liver metastases, PET-CT identified unexpected extra-hepatic disease not detected on conventional imaging which led to a change in the surgical management of 17% of the patients. For the detection of extra-hepatic sites of disease, FDG PET-CT has a reported sensitivity and specificity of 91.5% and 95.4%, respectively [27].

Liver metastasis is the main cause of death in patients with colorectal cancer and about 35–55% of patients develop hepatic metastases during the course of their disease [28]. For selected patients with colorectal cancer metastases limited to the liver, hepatic resection is the standard of care and may be curative with a 5-year survival of greater than 30% [29]. Therefore accurate identification of the number, size, location and characterization of hepatic lesions is essential for the final therapeutic decision. In a meta-analysis by Bipat et al. [30], the sensitivities of helical CT, 1.5T MR and 18FDG-PET on a per-patient basis were reported at 64.7%, 75.8%

and 94.6%, respectively. On a per-lesion basis, the sensitivities for the three modalities were 63.8%, 64.4% and 75.9%, respectively. In this respect, PET-CT offers the best combination of sensitivity and specificity amongst all the available techniques.

Despite its superior performance, unenhanced PET-CT cannot replace contrast enhanced MRI for the detection of liver metastases [31] and in particular for smaller lesions, as PET-CT is limited by its intrinsic resolution and at times by the variable metabolic 18FDG activity of mucinous tumours. In this regard, contrast-enhanced MRI with gadolinium [32] manganese dipyridoxyl diphosphonate (MnDPDP) [26] or gadolinium methoxybenzyldiethylenetriamine pentaacetic acid (GdEOBDTPA) [33] has been shown to be highly sensitive. If surgical resection is planned then a dedicated contrast-enhanced MRI should be performed in addition to a PET-CT for all patients with potentially resectable hepatic metastases as a prerequisite, preoperative assessment tool (Figs. 4.4 and 4.5).

About 10–25% of patients with colorectal cancer develop pulmonary metastases but only a few of these have metastases confined to the lungs. In this group it is currently not possible to adequately identify those who may benefit the most from thoracotomy [18]. Claims for a survival benefit for patients undergoing this surgery rely on case series with little documentation of any symptoms attributable to pulmonary metastases that are alleviated or obviated by metastasectomy. A systematic review of pulmonary metastasectomy in colorectal cancer concluded that the quality

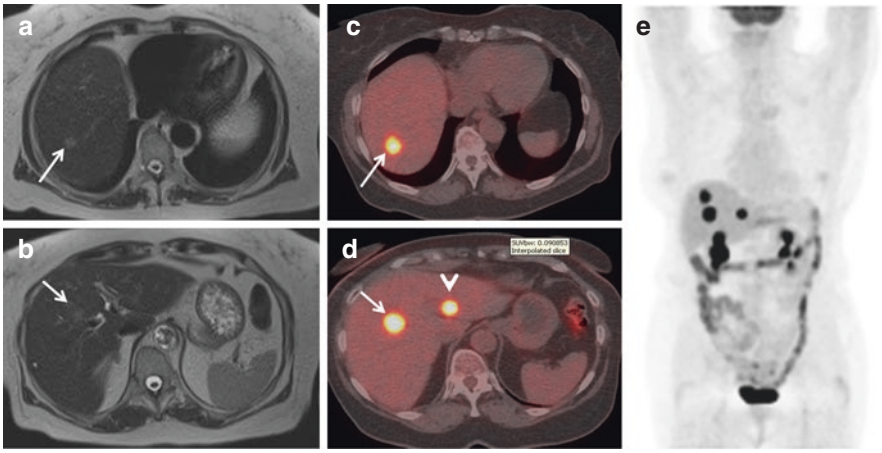

Fig. 4.4 Role of PET-CT in hepatic metastases. 75-year-old with previous right hemicolectomy. Conventional contrast enhanced MRI demonstrated two hepatic metastases seen here on the axial T2W images in segment 7 (arrow in **a**) and segment 4a (arrow in **b**). Fused PET-CT images however demonstrated three intensely FDG avid lesions, two corresponding to the lesions seen on MR (arrows in **c** and **d**) but in addition picked up a lesion in segment 2 (arrow head in **d**). The three liver lesions are clearly seen on the MIP mage (**e**). FDG PET-CT has complimentary role to MRI and can pick up lesions which can be missed on MRI

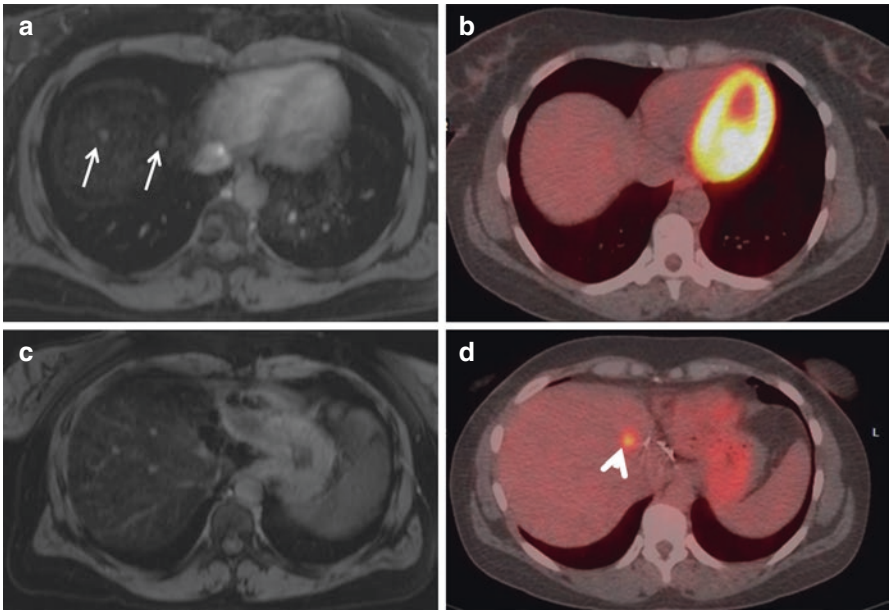

Fig. 4.5 Role of PET-CT in hepatic metastases. 37-year-old woman with colon cancer. Past history of hemicolectomy followed by left hemihepatectomy for liver metastases 7 months later. Follow up MRI done 5 months after hepatectomy demonstrates two subtle focal lesions consistent with metastases at the hepatic dome on the fat suppressed T2 images (arrows in **a**). Fused PET-CT failed to demonstrate the two sub cm lesions at the dome (**c**) but demonstrated a focal high intensity uptake at the resection margin (arrow head in **d**) in keeping with recurrent disease. This was however not seen on MRI likely secondary to metallic artefacts. Artefacts form the surgical staples can make MR assessment difficult; while smaller lesions can be below the sensitivity of PET-CT thus emphasising the complimentary role of the two modalities for complete assessment of the liver

of evidence available is not sufficient to draw inferences concerning the effectiveness of this surgery. Given the burdensome nature of the surgery involved, better evidence, ideally in the form of a randomized trial, is required for the continuance of this practice [34]. For the detection of pulmonary metastases, a breath holding diagnostic CT remains the mainstay for diagnosis. The limitations on PET-CT are potential false negatives due to the small size of the lesions below the resolution of conventional PET-CT scanners exacerbated by a non-breath hold/non-gated imaging technique. We therefore recommend caution in the interpretation of PET-CT images in light of the conventional imaging where suspicious pulmonary lesions on CT should be considered metastatic even if they are not FDG avid, particularly if they are new and increase in size over time (Figs. 4.6 and 4.7).

In summary, 18F-FDG PET-CT should be used routinely in addition to conventional imaging in the preoperative diagnostic work-up of patients with potentially resectable hepatic and pulmonary metastases from colorectal cancer where the addition of PET-CT can potentially avoid futile surgeries.

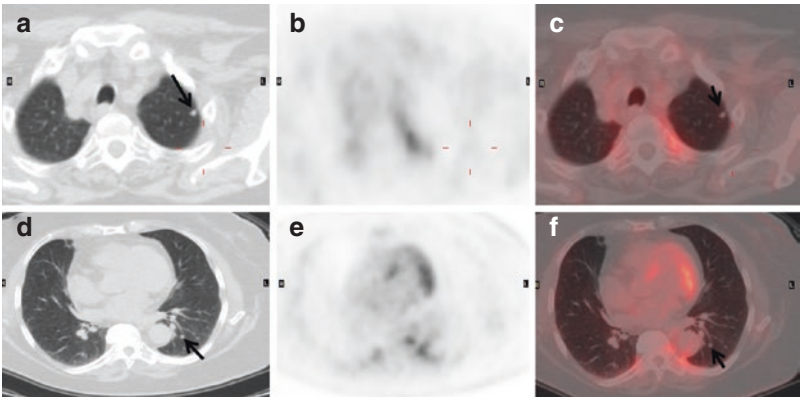

Fig. 4.6 FDG PET-CT in suspected pulmonary metastases from colorectal cancer. 70-year-old male with caecal cancer and multiple tiny lung nodules 4–6 mm in size seen for example in the left upper lobe (arrow in **a**) and left lower lobe (arrow in **d**) on the axial CT sections. There was no corresponding FDG uptake on the fused images (arrows in **c** and **f**). This is likely due to the small size of the nodules which is below the resolution of routine FDG PET-CT (<7 mm). Based on the typical CT appearances these nodules should be considered suspicious for metastases even though not FDG avid

Limitations of FDG PET-CT in Colorectal Cancer Metastases

PET has a spatial resolution of 5–7 mm and therefore has limited sensitivity in characterizing small metastases. Certain tumours as already mentioned such as mucinous adenocarcinomas can be falsely negative due to their limited FDG uptake and it is postulated that FDG PET-CT might be insensitive in demonstrating mucinous carcinomas also because of the typically low cellularity of these tumours [35, 36]. The sensitivity of FDG PET-CT for the detection of metastases (particularly if <1 cm) is also lowered in patients treated by neoadjuvant chemotherapy and studies have shown that contrast-enhanced CT is more sensitive than FDG PET-CT in this setting [37].

Despite the limitations of FDG PET-CT, studies have shown it to be a cost effective modality in this subgroup of patients. A study by Lejeune et al. [38] aimed to compare the cost effectiveness of standard imaging techniques with and without FDG PET-CT in the management of metachronous liver metastases from colorectal cancer using a decision analysis mode. These authors showed that PET- CT was the most cost effective strategy within the diagnostic group. Another study by Zubeldia and colleagues [39] demonstrated that integration of FDG PET-CT into the presurgical evaluation of patients with hepatic metastases resulted in substantially reduced overall costs and patient morbidity. This finding results from the unique ability of FDG PET-CT to exclude patients with extra-hepatic disease thereby avoiding unnecessary surgery.

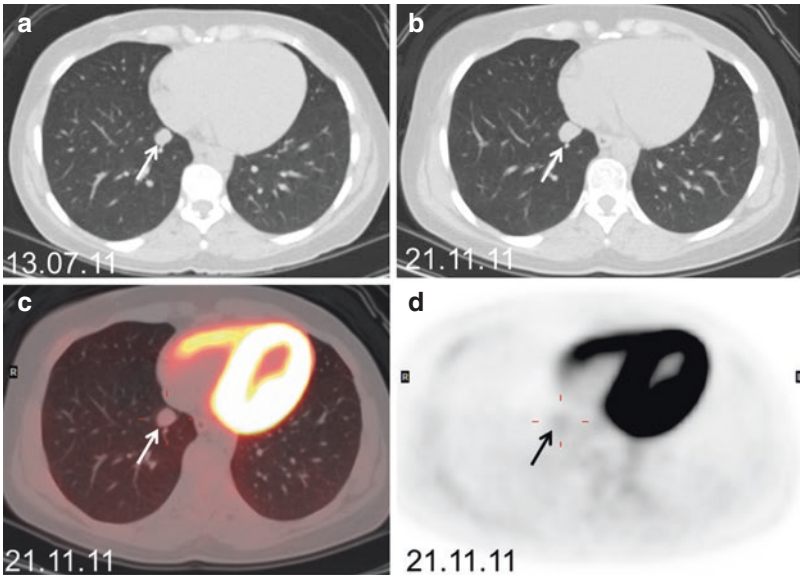

Fig. 4.7 FDG PET-CT in suspected pulmonary metastases from colorectal cancer. 55-year-old female with rectal cancer treated with long course CRT and APR. Initial staging CT had revealed a 1.7 cm size right lower lobe lung nodule (arrow in **a**). Follow up CT showed increase in size of the nodule to 2.1 cm (arrow in **b**) however the nodule continued to demonstrate only very low intensity uptake below the blood pool seen on the fused (arrow in **c**) and attenuation corrected images (arrow in **d**). The histology of the primary tumour was a mucinous adenocarcinoma which is known to be of low cellularity and thus show low to no FDG uptake. The typical CT picture and increase in size were keeping with a slowly enlarging metastasis even though not FDG avid, this was subsequently resected and confirmed

FDG PET-CT in the Management of Colorectal Cancer Patients with Recurrent Disease

FDG PET-CT is now considered the standard of care for detecting and staging suspected recurrence of colorectal carcinoma and has a direct impact on patient management in up to two-thirds of cases [24]. Recurrent disease is a major contributor to mortality in colorectal cancer patients and can be seen in up to one-third of patients usually within 3 years of curative surgery [40, 41]. Patients with rectal cancer appear to be at a higher risk (11.3%) of local recurrence when compared with patients with colon cancer (6.1%) [42] where systematic postoperative surveillance will affect outcome [43].

Recurrence can be suspected either clinically (based upon patient symptoms) or on routine follow-up including on a CT and as part of screening protocols utilizing serial serum carcinoembryonic antigen (CEA) levels. However, approximately 7% of patients undergoing serial serum CEA measurements have elevated values in the presence of apparently normal or equivocal CT scans [44]. In this context, CEA is not a good indicator of tumour activity in all patients and recurrent disease can of

course be found in some patients with normal CEA levels. The characterization of suspected local recurrence (defined as abnormal soft-tissues at or near the site of a treated tumour and which include peri-anastomotic tissue, presacral tissue and local nodes), is based upon a combination of findings including recognition of the pattern of uptake, the intensity of uptake, the time interval since previous surgery and other ancillary PET-CT findings. Local lesions are considered as positive for recurrence if they demonstrate focal, high-intensity FDG uptake persisting for several months after surgery (Fig. 4.8). Those local lesions without an abnormal increase in FDG uptake or with a diffuse peripheral low-grade uptake recognized soon after surgery are considered benign and likely due to an inflammatory response rather than recurrence (Figs. 4.9 and 4.10). Enlarging solid local masses and pelvic nodes with intermediate to high intensity FDG uptake are also generally regarded as signifiers of recurrent disease (Fig. 4.11).

As already mentioned, PET is limited by its lack of spatial resolution and because small-volume disease may not appear avid [45]. PET-CT images are also susceptible to mis-registration artefacts. Physiological FDG uptake in displaced pelvic organs such as the bladder, small bowel loops, seminal vesicles and the uterus can also account for erroneous interpretation [46]. The differentiation between local post-treatment change and recurrence can be extremely difficult on both CT and MR. CT is the modality most often employed in the detection of local recurrence with reported sensitivities of between 82% and 88%, with a specificity of 50–97% and an accuracy of 68–96% [47, 48]. MR imaging has a reported sensitivity of 87–91%, a specificity of 86–100% and an accuracy of 87.5–95% in the diagnosis of local recurrence. Several of these studies are summarized in Table 4.2 which evaluate the role of PET or PET-CT in the detection of pelvic recurrence [46, 49–52]. A meta-analysis by Maas et al. [20] concluded that PET-CT might be the modality of choice in evaluating such patients.

Although high sensitivity and specificity rates have been reported for PET-CT in the detection of local recurrence, MR imaging should be performed in patients being considered for surgery. MR, due to its high soft-tissue resolution, provides information on anatomic location and the extent of the local lesion, which guides surgical planning. In this regard, there is little published data concerning the pattern of uptake in FDG PET which would most reliably predict a surgically amenable anastomotic recurrence (Fig. 4.12). In one study, [51] the presence of an eccentric or peri-anastomotic mass on CT with a corresponding eccentric or peri-anastomotic FDG uptake on PET was the most reliable PET/CT uptake pattern predictive of a staple line recurrence.

CEA, which is widely used in the surveillance of post-operative colorectal cancer patients, is pragmatically hampered by a false-positivity rate between 10% and 30% [53]. In this respect, data from several studies as summarized in Table 4.3, suggest that PET-CT has a role in the detection of occult recurrent disease in patients with an unexplained rise in their CEA levels (Figs. 4.13 and 4.14). Most such stud-

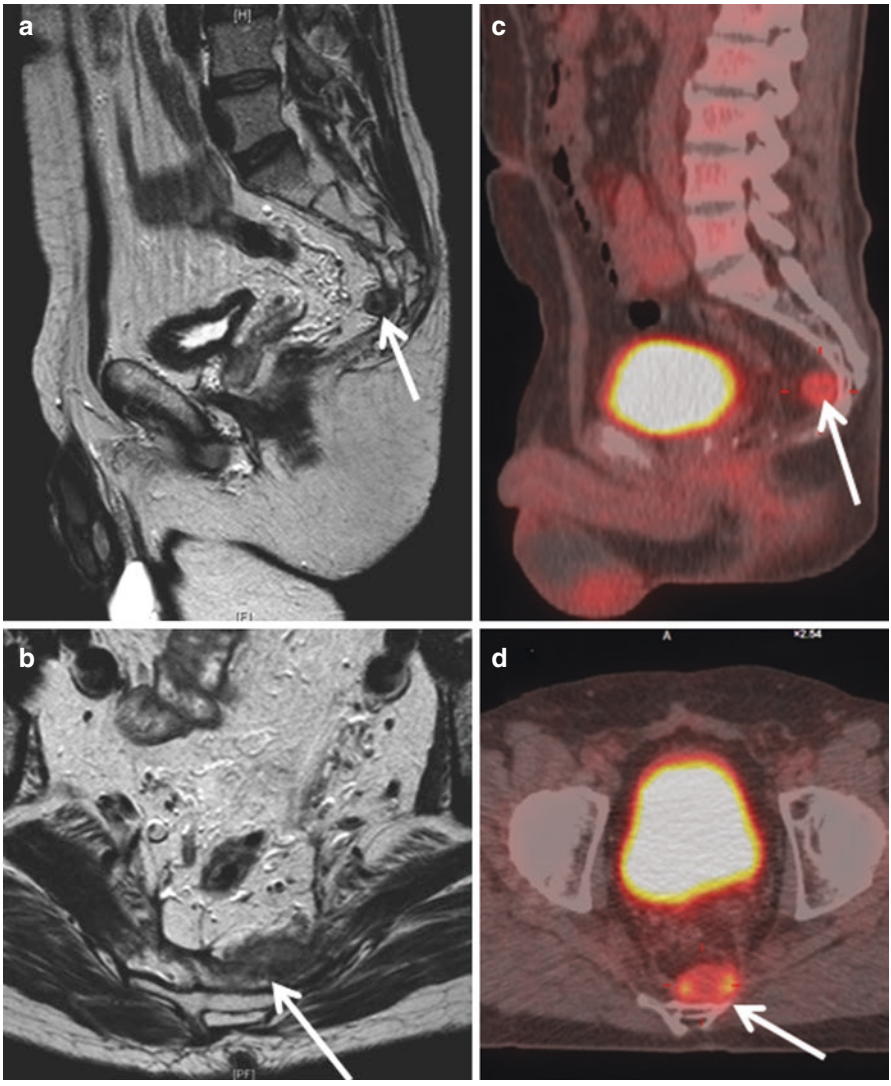

Fig. 4.8 Role of FDG PET-CT in recurrent colorectal cancer. 57-year-old male with previous low anterior resection and clinical suspicion of local recurrence. MR imaging on T2 W sagittal (**a**) and axial (**b**) planes demonstrate a suspicious intermediate signal rounded lesion in the presacral soft tissues. Fused FDG PET-CT images in corresponding plane demonstrate very high intensity focal eccentric uptake (arrows in **c** and **d**) in this soft tissue lesion consistent with recurrent disease. FDG PET-CT has high accuracy in characterization of indeterminate presacral masses

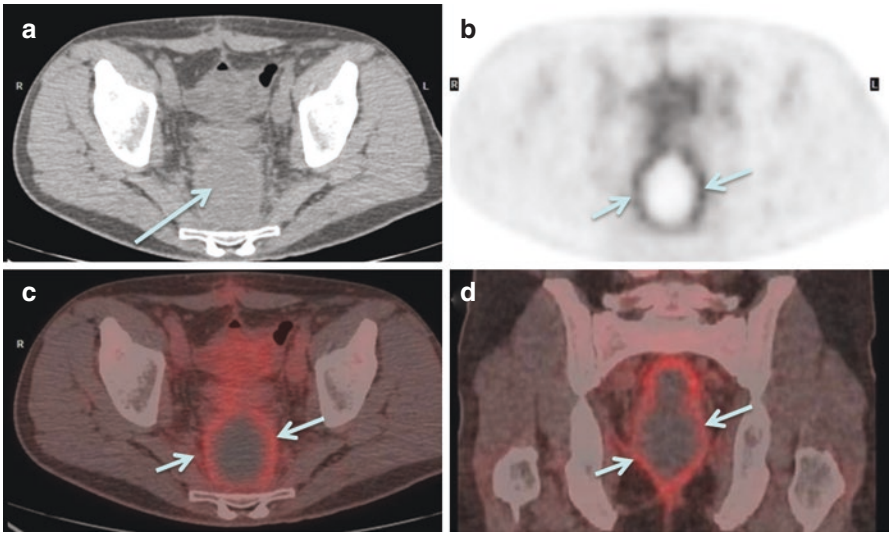

Fig. 4.9 Role of FDG PET-CT in recurrent colorectal cancer. 50-year-old with man with suspected recurrence following abdominoperineal resection for rectal cancer. FDG PET-CT performed 8 weeks post-surgery. Axial CT (**a**) demonstrates a presacral abnormality with central low density (long arrow). Axial PET image (**b**) and fused PET-CT images in the axial (**c**) and coronal planes (**d**) demonstrate symmetrical diffuse peripheral low grade uptake in the walls of the cavity (short arrows). Note the absence of any nodular areas of asymmetrical high intensity uptake and the usefulness of the coronal plane to demonstrate the entire extent. Above appearances are typical for a post-surgical inflammatory collection/abscess with no evidence to suggest local recurrence

ies have shown high positive predictive values [52–57]. A clinical trial by Sobhani et al. [58] has also examined the potential use of FDG PET as a surveillance imaging technique in colorectal cancer patients. Results of this trial showed that not only that PET allowed for an earlier diagnosis of relapse, but also that the rate of successful surgery with curative intent (designated R0) was significantly higher in the PET-managed group. FDG PET-CT should be used early in the evaluation of patients with treated colorectal cancer and even possibly as a systematic surveillance technique in high-risk patients, especially during the first 2 years after initial treatment at a time when 80% of recurrences will develop.

The management of colorectal patients with rising CEA levels and a clinical suspicion of recurrence but with negative conventional imaging and PET-CT remains an ongoing challenge. There may be a role in such patients for performing dual time point PET-CT for problem solving in order to improve the sensitivity of lesion detection by creating a longer delay between the injection of the tracer and image acquisition (Fig. 4.15). This allows for a higher tumour-to-background ratio probably related to an increased glucose uptake through glucose transporters with a low concentration of glucose-6-phosphatase activity in the tumour cells. In contrast,

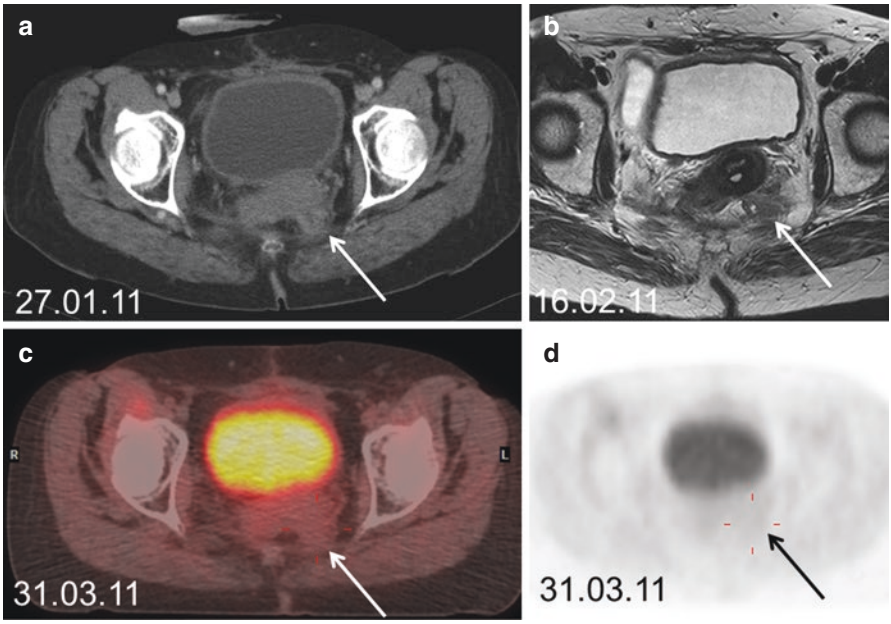

Fig. 4.10 Role of FDG PET-CT in recurrent colorectal cancer. 61-year-old female with rectal carcinoma treated with long course chemoradiotherapy followed by low anterior resection. Follow up axial contrast enhanced CT (**a**) showed indeterminate nodular soft tissue in the left posterior pelvis (arrow). Subsequent MR (**b**) also revealed an ill-defined soft tissue at this site with heterogeneous signal (arrow in **b**), Local recurrence could not be excluded and a CT guided biopsy was being considered. Following MDT discussion radiologist advised a PET-CT prior to attempting biopsy. This clearly showed that the area of concern did not show any abnormal increased uptake (arrows in **c** and **d**). Findings were in keeping with a benign abnormality. External operative notes showed at the time of surgery there was a very dense adhesion of the low rectum and the left posterolateral aspect; however, the CRM was negative and findings would be in keeping with a resolving haematoma. This was proven on follow up. FDG PET-CT has a high negative predictive value for recurrent disease and in this case helped avoid an unnecessary biopsy

such a prolonged period of FDG uptake is rare in normal tissues. It has been shown by Kuker et al. [59] that FDG PET scans 120 min after injection will detect hepatic lesions that have been missed in 17% of the images obtained only 90 min following injection. Similar studies showing accumulation of FDG in malignant tumours for prolonged periods after intravenous administration have been published [60, 61]. There is also evidence from recent studies which suggests that the addition of intravenous contrast to the CT component of the PET-CT significantly improves its sensitivity, specificity and accuracy of the PET-CT in the detection of recurrent colorectal cancer [12, 62], yielding important additional tumour-related information.

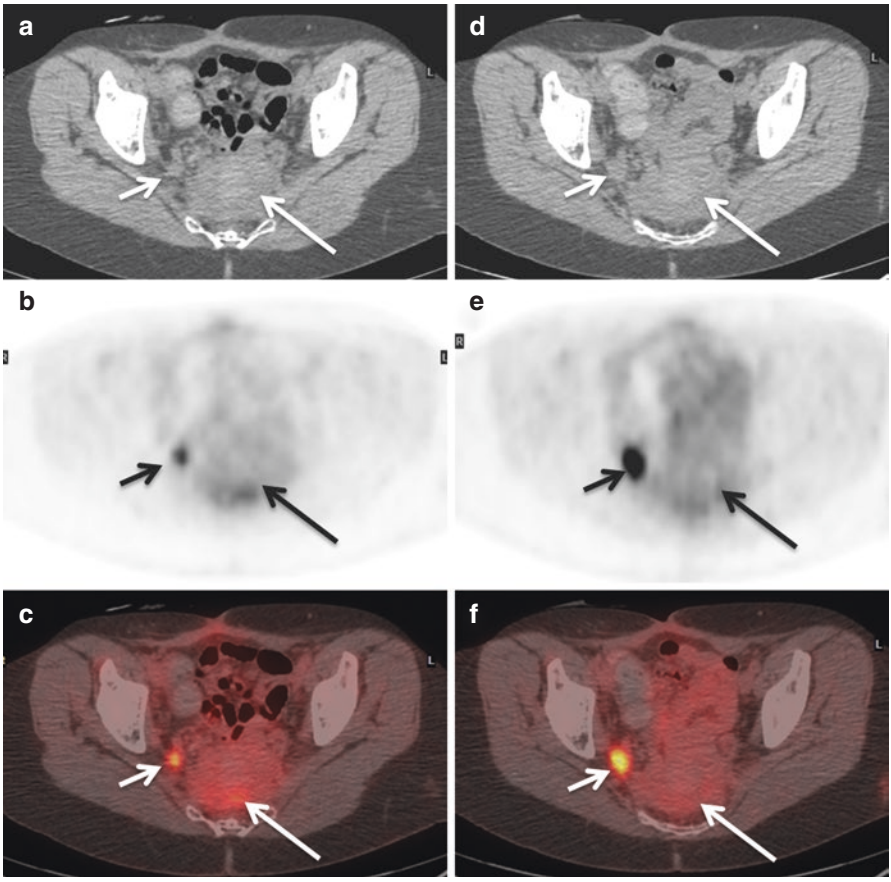

Fig. 4.11 Role of FDG PET-CT in recurrent colorectal cancer. 65-year-old female with suspected recurrent colorectal cancer after long course chemoradiotherapy and low anterior resection for rectal cancer. Axial CT (**a**), FDG PET (middle) and fused (bottom) images of a FDG PET/CT scan. First follow up PET-CT with CT (**a**), attenuated corrected (**b**) and fused (**c**) images performed 6 weeks after surgery demonstrates presacral soft tissue with low intensity FDG uptake (long arrow) presumed to represent post treatment inflammatory uptake. A sub-cm right internal iliac node with intermediate intensity uptake (short arrow) is suspicious but remained indeterminate between a reactive or malignant node. Subsequent follow up FDG PET-CT with CT (**d**), attenuated corrected (**e**) and fused (**f**) images performed after 3 months demonstrates decrease in intensity of FDG uptake within a stable presacral soft tissue mass (long arrow) consistent with post treatment fibrosis. However, there is increase in both intensity of FDG uptake and size of the right internal iliac node (short arrow) consistent with malignant nodal uptake in keeping with recurrent nodal disease

Table 4.2 Comparative studies on the performance of FDG PET or PET-CT in suspected colorectal local recurrence

Studies	Imaging modality	Number of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Even-Sapir et al. [46]	PET	62	82	65	73	75	74
Moore et al. [49]	PET/CT	60	84	88	76	92	87
Shyn et al. [51]	PET/CT	77	100	97	82	100	98
Fukunaga et al. [50]	PET/CT	42					93
Liong et al. [52]	PET/CT	44	100	84	89	100	93

PPV positive predictive value, *NPV* negative predictive value, *PET/CT* positron emission tomography/computed tomography

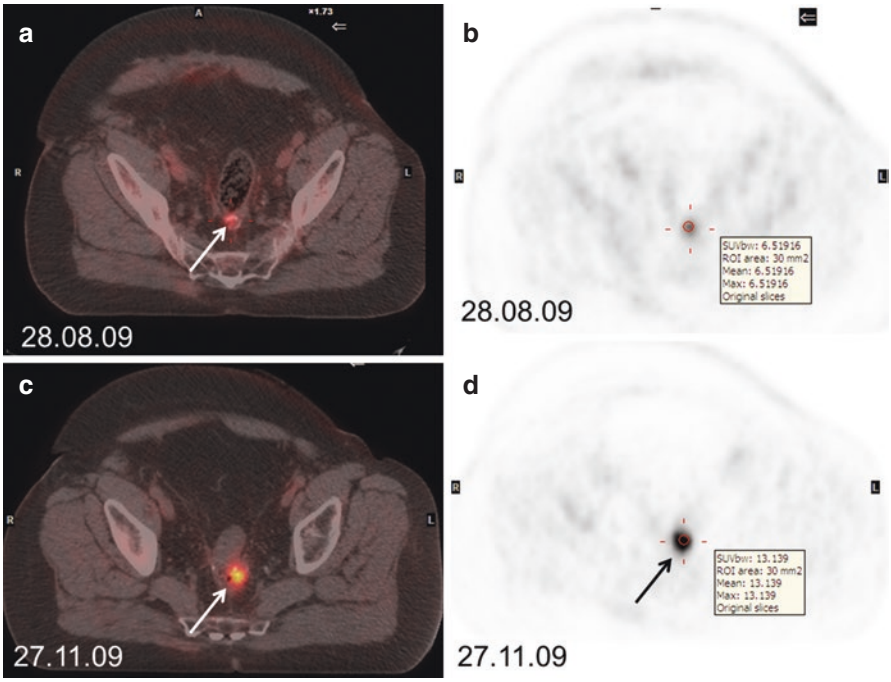

Fig. 4.12 Role of FDG PET-CT in recurrent colorectal cancer. 75-year-old male with sigmoid adenocarcinoma treated with anterior resection. A FDG PET-CT was performed prior to surgical resection of a small liver lesion. Axial fused PET-CT image (**a**) and attenuated corrected image (**b**) demonstrated a focus of intermediate intensity uptake at the anastomotic margin (arrows). At that point (approximately 6 months post-surgery) it was not clear if this was persistent inflammatory uptake or recurrence. Follow up PET-CT 3 months later demonstrates persistent focal high intensity uptake increased compared to previous located eccentrically at the anastomotic line consistent with recurrent disease (arrows in **c** and **d**) which was subsequently confirmed on sigmoidoscopy. Early recurrence at the anastomotic line can be difficult to accurately characterize on conventional imaging modalities

Table 4.3 Comparative studies on the performance of FDG PET or PET-CT in suspected colorectal cancer recurrence in the context of an elevated carcinoembryonic antigen levels

Studies	Imaging modality	Number of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Flanagan et al. [53]	PET	22			85	97
Maldonado et al. [54]	PET/CT	72	94	83	97	71
Flamen et al. [55]	PET/CT	50	79		89	
Shen et al. [56]	PET/CT	40	95			
Kyoto et al. [57]	PET/CT	57	93	74	91	98
Liong et al. [52]	PET/CT	18	79	67	92	40

PPV positive predictive value, *NPV* negative predictive value, *PET/CT* positron emission tomography/computed tomography

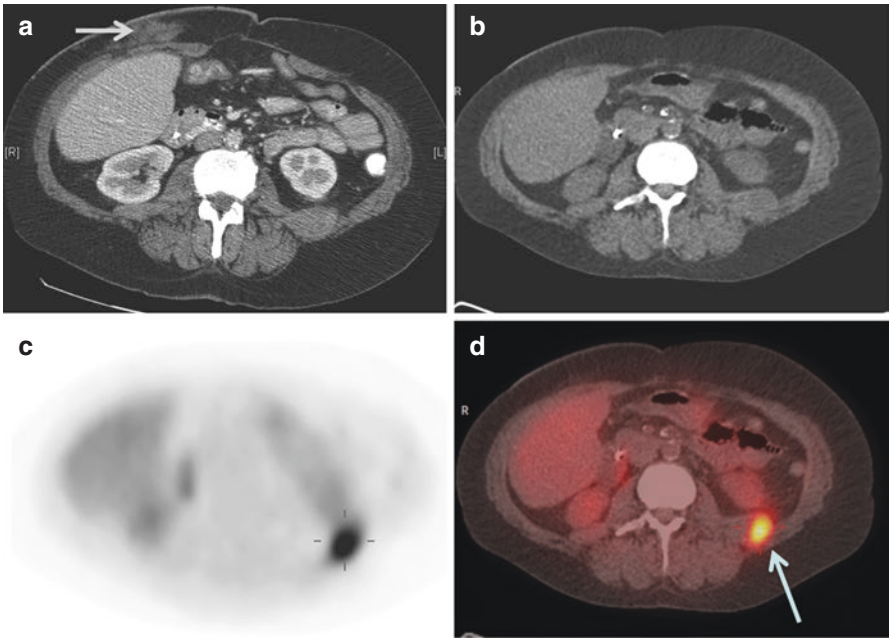

Fig. 4.13 Role of FDG PET-CT in patients with unexplained rising CEA levels. 55-year-old female with previous sigmoid cancer and rising CEA levels. Contrast enhanced CT (**a**) was reported as being unremarkable. Stranding noted at site of reversal of ileostomy (arrow). FDG PET-CT with unenhanced CT (**b**), attenuation corrected (**c**) and fused images (**d**) demonstrate an intensely FDG avid focus of uptake in the left quadratus lumborum muscle (arrow in **d**) confirmed to represent an intramuscular metastasis. On retrospect on CT asymmetry in the muscle bulk due to a soft tissue lesion can be seen. FDG PET CT is a useful problem solving tool to identify potentially occult causes for rising CEA

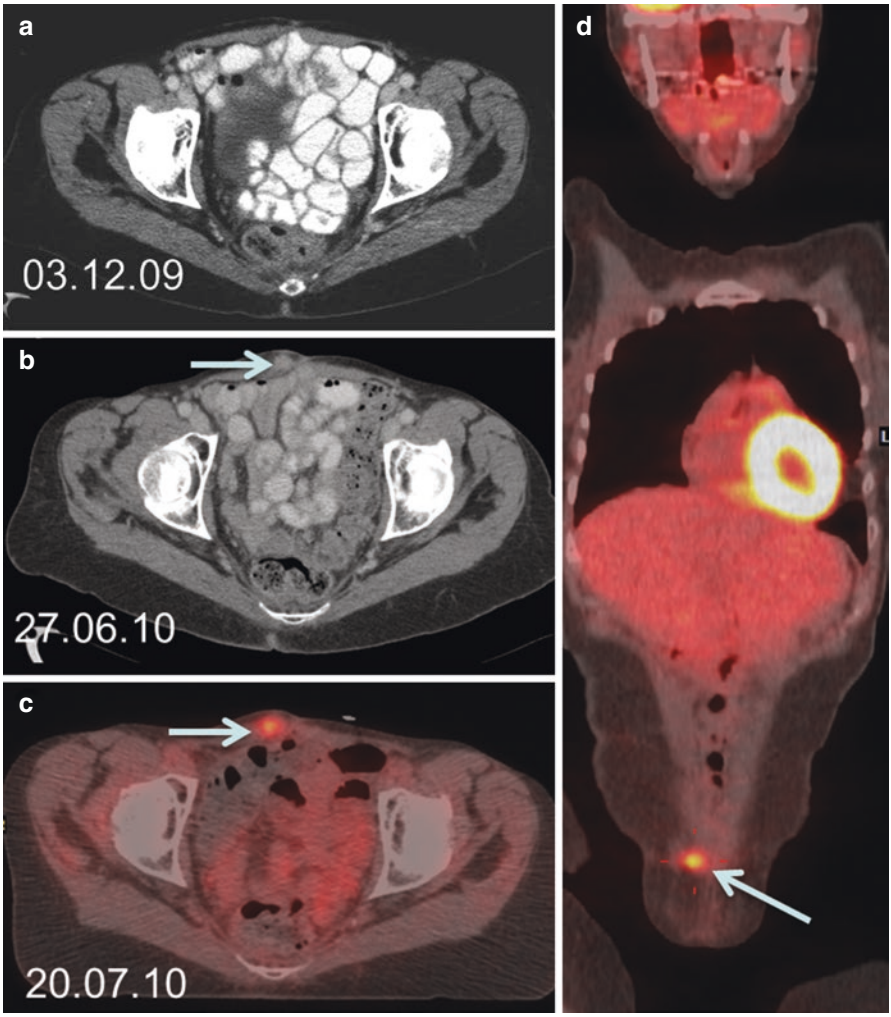

Fig. 4.14 Role of FDG PET-CT in patients with unexplained rising CEA levels. 78-year-old female with colorectal carcinoma and peritoneal metastases which were treated with cytoreduction and HIPEC with a complete resection. Rising tumor markers. First follow up contrast enhanced CT (**a**) was unremarkable. Subsequent follow up CT at 6 months (**b**) failed to report a subtle anterior abdominal wall nodule (arrow). Fused PET-CT image (**c** and **d**) clearly demonstrate an enlarging FDG avid nodule (arrows). This was resected and was confirmed as an abdominal wall implantation metastasis. Patient is on follow up and remains disease free

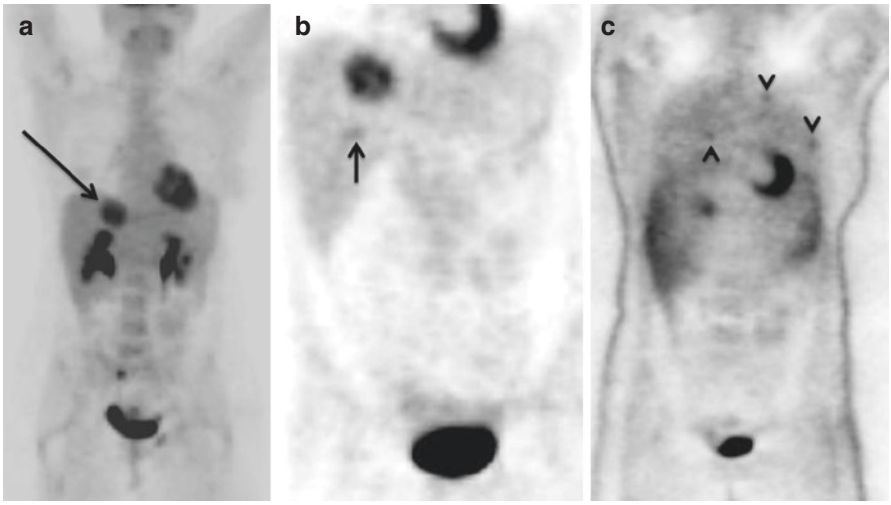

Fig. 4.15 Role of dual time point FDG PET-CT. 70-year-old female with colorectal cancer and known solitary liver metastasis presenting with rising CEA levels. Conventional imaging confirmed the known solitary hepatic metastasis but failed to demonstrate any evidence of disease progression to explain the rising CEA levels. Routine FDG-PET 1 h post injection (**a**) also demonstrates a solitary FDG avid hepatic lesion (long arrow). Delayed FDG PET performed at 2 h (**b** and **c**) post injection however demonstrates a further suspicious FDG avid hepatic lesion (short arrow in **b**) and several pulmonary micro-nodules with increased FDG uptake which are better seen on the non-attenuation corrected (NAC) images (arrow heads in **c**)

FDG PET-CT for Peritoneal Metastases from Colorectal Cancer

Peritoneal metastases can occur in 10–30% of gastrointestinal cancers but they are more frequent those patients presenting with recurrent disease. Peritoneal metastases have been historically regarded as a terminal development with a median survival of between 5 and 12 months after treatment with systemic chemotherapy [63]. If metastatic disease is limited to the peritoneal cavity then in selected cases cytoreductive surgery combined with heated intraperitoneal chemotherapy (HIPEC) can potentially improve the prognosis with survival reaching up to 60 months in some studies [64]. Traditionally the gold standard for the detection of intraperitoneal disease has been surgical exploration of the peritoneal cavity (or laparoscopy) but the imaging of this small volume disease has proven a major challenge. In some cases, this is due to the variable appearances of deposits as well as the small size of individual lesions which can be invaginated into the peritoneal reflections or which may coat the bowel surface and which are extremely difficult to distinguish from adjacent structures. FDG PET-CT has the potential to improve the detection of peritoneal metastases as lesion conspicuity is relatively high on PET due to the typically

low background activity and fused PET-CT imagery offers the combined benefits of anatomic and functional imaging. Distinct patterns appear to predict the presence of either nodular or diffuse peritoneal pathology (Fig. 4.16). The main pitfalls are related to the normal physiologic activity inherent in bowel loops and blood vessels and the focal retained activity localized in the ureters. Amongst the various described scintigraphic signs, focal uptake was observed to be the principal indicator of peritoneal metastases where it was detected in 86% of cases in a study by Bullier et al. [65]. Patients with a primary mucinous histology can as with other areas of locoregional recurrence show falsely negative results on PET consequent upon their low cellularity, however, this pitfall can usually be circumvented by a careful review of the CT component of the study (Fig. 4.17). Although there are several studies which address the performance of PET-CT in the detection of peritoneal metastases, only limited data are available concerning its role in accurately detecting the true extent of peritoneal disease. This information is essential for the surgeon to judge the completeness of resection in patients, particularly delineating the presence and extent of small intestinal and mesenteric involvement, gross infiltration of the hepatogastric

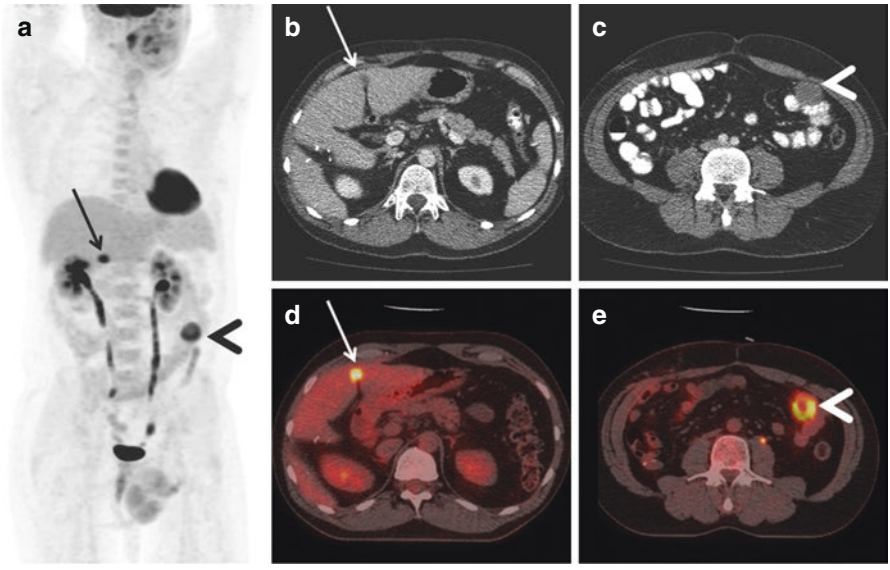

Fig. 4.16 Peritoneal metastases from colorectal primary. 47-year-old male with colonic cancer previously treated with right hemicolectomy and liver resection presented 1 year later with suspected solitary peritoneal metastases on CT. Axial CT demonstrated the left anterior flank deposit (arrow in **c**) however a subtle low attenuation deposit in the falciform ligament (arrow in **b**) was not picked up however is clearly seen as an intensely FDG avid focus on the fused PET-CT image (arrow in **d**). MIP image (**a**) clearly shows both the deposits. PET-CT has superior accuracy than conventional CT in detecting peritoneal metastases

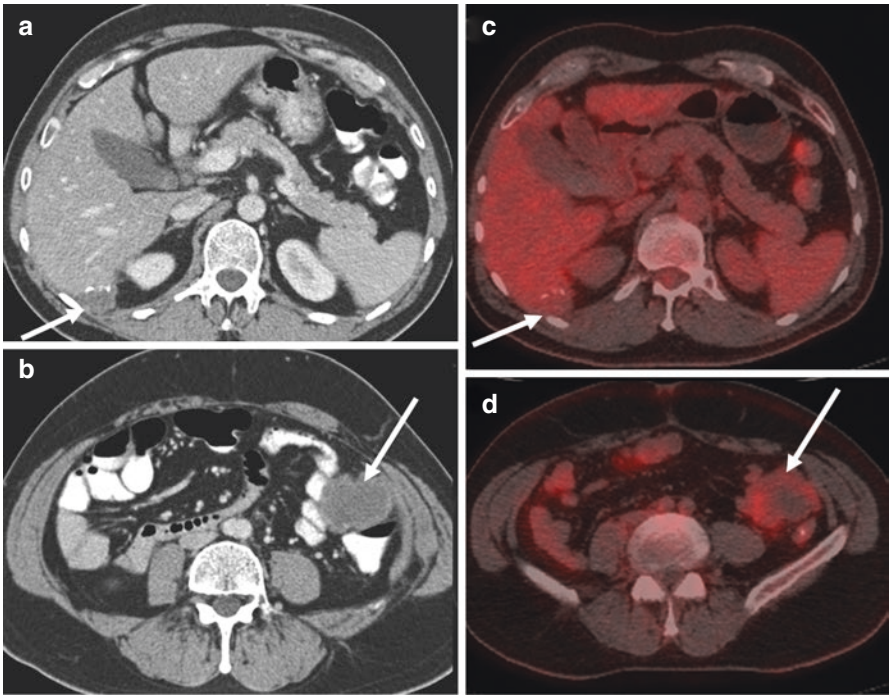

Fig. 4.17 Peritoneal metastases from a mucinous primary. 67-year-old male presented with a primary mucinous type adenocarcinoma of the sigmoid colon and developed peritoneal metastases. Axial contrast enhanced CT images (**a** and **b**) demonstrate low attenuation deposits in the left subhepatic space (arrow in **a**) and left paracolic gutter (arrow in **b**). FDG PET-CT images (**c** and **d**) do not show any abnormal increased uptake corresponding to these deposits. This is due to the low cellularity of the mucinous metastases and FDG PET-CT can be false negative in such cases which need careful assessment of the CT component for accurate assessment of the disease extent

ligament, involvement of the porta hepatis, the presence of unresectable pelvic sidewall disease and ureteric obstruction. Further studies are needed which compares the preoperative peritoneal carcinomatosis index (PCI) score with the surgical PCI score in order to define FDG PET-CT accuracy in this disease [66].

Comparison of FDG PET-CT to the performance of MRI with diffusion sequences indicates that PET/CT appears to be complementary to, (indeed in some studies is more accurate than), diffusion MRI [67] or DCE MRI [68]. All imaging techniques tend to underestimate the real extent of peritoneal metastases because of their generally low to medium sensitivity, particularly for lesions <1 cm in size. Our group, as a specialized National Centre for the management of peritoneal tumours utilizes laparoscopy as the gold standard of care in peritoneal metastasis detection defining the PCI index by experienced colorectal surgeons after discussion in specialist multidisciplinary team (MDT) meetings.

18F-FDG PET-CT for Response Assessment in Colorectal Cancer

Neoadjuvant chemoradiation (CRT) has been increasingly employed in the treatment of locally advanced rectal cancer (LARC). Pathological complete response is noted in up to 30% of patients undergoing this treatment and not surprisingly evidence suggests that a complete response is associated with a better overall oncologic outcome [69]. The key question raised is whether radical surgery should be necessary for patients with a clinical complete response to CRT or whether a 'watch and wait' policy is indicated [70]. Accurate radiological prediction of the histopathological tumour response could enable response-guided modifications of the treatment protocol. Clinical assessment after CRT is known to be quite unreliable and conventional imaging modalities cannot readily distinguish fibrosis or scar from viable tumour cells within residual masses [71]. As a result, emphasis has been on imaging modalities like PET-CT which provide a combination of metabolic and morphologic information and which could potentially predict histopathological response in patients with LARC after treatment with preoperative CRT.

Rectal cancer is a disease model of particular interest, not only for its high incidence, but also because an accurate and non-invasive method to evaluate response to preoperative CRT could lead to patient selection for minimally invasive surgical approaches or even selection of candidates for additional chemotherapy and observation without any kind of surgery [69]. To date, the literature is mixed with regard to the ability of 18-FDG-PET to predict response to neoadjuvant treatment in patients with rectal cancer. The majority of studies have reported post-treatment SUV to be lower than pre-treatment scans, but post treatment SUV has not been found to correlate with pathologic complete response (pCR). In a study by Palma and colleagues et al. [72]. which included 50 patients with LARC treated with preoperative CRT, all were evaluated by PET-CT before and after CRT and the results were compared with the histopathologic response quantified by the tumour regression grade. The study concluded that 18-FDG- PET-CT performed 5–7 weeks after the end of CRT can visualize functional tumour response in LARC, however, it is unable to accurately predict those patients with a pCR.

Another study by de Geus-Oei et al. [73] analyzed the difficulty in comparing the outcome of different studies because of the use of several methods to analyse response (namely, visual FDG-PET response, SUVmax, SUVmean, SUV ratio or even TLG – the change in total lesion glycolysis), and the effect of the timing of post CRT imaging. In this study, the time interval between the end of CRT and surgery and the time interval between the end of CRT and the post-treatment PET-CT scan represent two discrete variables which have not been previously investigated both of which have the potential to affect the ability of PET-CT scans to predict the CRT response.

Conclusion

FDG-PET-CT imaging now has an established role in the management of patients with colorectal cancer. For clinical practice, FDG PET-CT is the modality of choice when evaluating patients with a suspicion of recurrent disease largely because of its high accuracy in detection and its ability to characterize recurrent disease. FDG-PET-CT imaging is valuable as a problem-solving tool in the evaluation of patients with rising tumour markers in the absence of a known source and where there is an inconclusive conventional diagnostic workup. The addition of FDG-PET-CT to the evaluation of patients with potentially resectable metastatic disease reduces overall treatment costs by accurately identifying patients who will benefit from surgical procedures. FDG PET-CT has a key role in infleuencing clinical management by guiding further procedures (biopsy, surgery, and radiation therapy), in response assessment and specialized treatment planning.

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Part III
Pathology

Chapter 5
Pathology of Rectal Cancer and Predictors of Response to Neoadjuvant Therapy

Mariana Berho and Pablo Bejarano

Introduction

It has been reproducibly shown that rectal cancer patients managed by a multidisciplinary team of physicians yield better outcomes [1, 2]. The pathologist along with the surgeon, the medical oncologist and the radiation oncologist plays a key role in this team. The pathologist's role is important at all stages of patient treatment; namely: the preoperative stage confirming a diagnosis of malignancy on biopsy specimens, the intraoperative stage evaluating the distal margin of resection and the postoperative stage in the examination of the surgical specimen. The anatomical extent of the disease as determined by the pathological stage, the depth of tumor infiltration into the wall of the rectum and the status of the mesorectal lymph nodes have traditionally been the most important parameters guiding postoperative treatment.

In recent decades it has become apparent that the quality of the surgery, in part reflected by the integrity of the mesorectum excision has a significant impact on the incidence of both local and distant recurrences. Moreover, a shift from the distal to the circumferential margin of resection as the most influential factor in predicting local recurrence has become clearly evident. In this respect, the participation of the pathologist in the multidisciplinary team is well established in many centers in Europe, with a rather slow but general acceptance of this point across the United States. Regrettably, the pathologist's participation in the treatment of patients with rectal cancer worldwide still remains somewhat limited. One of the reasons for this absence is the historical tendency of pathologists to practice their work to a degree isolated from the rest of the health care providers involved in the management plan. In order to ensure comprehensive and effective care for this population of patients, this approach needs to be modified incorporating the pathologist as an integral part

M. Berho (✉) · P. Bejarano
Department of Pathology and Laboratory Medicine, Cleveland Clinic Florida, Weston, FL, USA
e-mail: berhom@ccf.org

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of the MDT. This labor can only be accomplished by full acceptance of this principle not only by the pathologist but also by clinicians and surgeons alike. It is therefore imperative to build educational programs that raise awareness around the fundamental role of the pathologist where this type of educational activity and approach have proven exceptionable value in centers in Europe. This chapter focuses in detail on the pathological evaluation of rectal cancer specimens, including gross and microscopic aspects as well as the basic concepts related to molecular characterization of these tumors.

Macroscopic Evaluation of the Rectal Cancer Surgical Specimen

Several studies have demonstrated that certain macroscopic and histological features have the capacity to reflect the quality of the surgery as delivered by the surgeon. These features can be readily recognized by most pathologists at the time of gross and microscopic examination and specifically include:

1. The integrity of the mesorectum.
2. The status of the resected margins with special emphasis on the circumferential margin of resection (the CRM) and
3. The number of dissected lymph nodes.

Mesorectal Quality/Plane of Surgery

The two major events responsible for the significant decrease in the episodes of pelvic recurrence in recent decades in patients with rectal cancer include the widespread acceptance of total mesorectal excision (TME) as a standard of operative care and the introduction of neoadjuvant chemoradiation [3, 4]. Local recurrence, although reduced still occurs and represents a major surgical challenge, in addition to significantly negatively impacting patient outcomes. In concert with the TME concept, it has become evident that the integrity of the mesorectum within the surgical specimen is one of the most critical prognostic factors for both local and systemic relapse [5–8]. The integrity of the mesorectum is directly related to the plane of surgical dissection and the separation of the rectum from the perirectal soft-tissues of the pelvis, based on the anatomical and embryological concepts advanced by Heald [9, 10]. In this widely accepted approach, the plane of surgery is identified at the mesorectum, within the mesorectum (intra-mesorectal) and at the muscularis propria (intramuscular). Based upon the latter anatomical view, the quality of the mesorectal excision (or the specimen mesorectum) can be classified as follows: [11, 12].

1. *Complete/mesorectal plane of surgery*: Intact mesorectum with minimal surface defects or defects in the mesorectal fat less <5 mm with no coning towards the distal margin of the specimen. The CRM is smooth on slicing (Fig. 5.1).

2. *Near complete/intramesorectal pla*ne: Tissue defects larger than 5 mm but without exposure of the muscularis propria (Fig. 5.2).
3. *Incomplete/muscularis propria plane*: Deep defects involving the mesorectal fat that lead to exposure of the muscularis propria. This latter situation carries the highest risk of recurrences as the remaining tissue in the pelvic cavity may contain residual cancer cells. There is little bulk to the mesorectum in these cases with a highly irregular CRM.

These categorizations are modified for abdominoperineal excisions such that:

Complete – the specimen shows a complete circumferential component of striated muscle at the levator insertion point

Near complete – there is no striated muscle with the resection margin formed by the muscularis propria

Incomplete – at the levator insertion point there is no muscularis propria and there may be perforations of the wall and in some cases evident surface tumor

Margins of Resection

Distal Margin

In 1908 Sir Ernest Miles published his landmark article in which he introduced the abdominoperineal resection operation to achieve cure in patients with rectal cancer [10, 13]. At the time the prevalent thought was that rectal cancer recurred mostly due

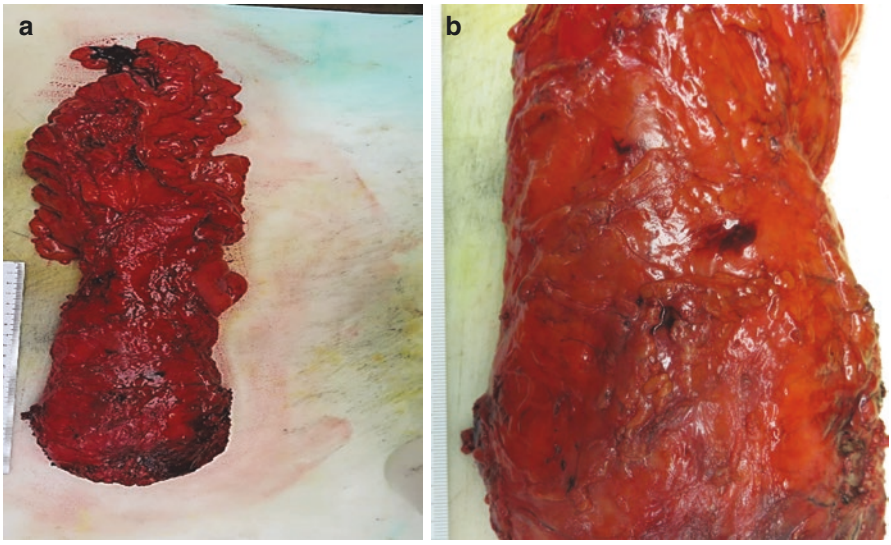


Fig. 5.1 (**a**) Complete mesorectum, anterior surface, no tears or defects are noted. (**b**) Complete mesorectum, posterior surface, bulky mesorectum with no exposure of the muscularis propria

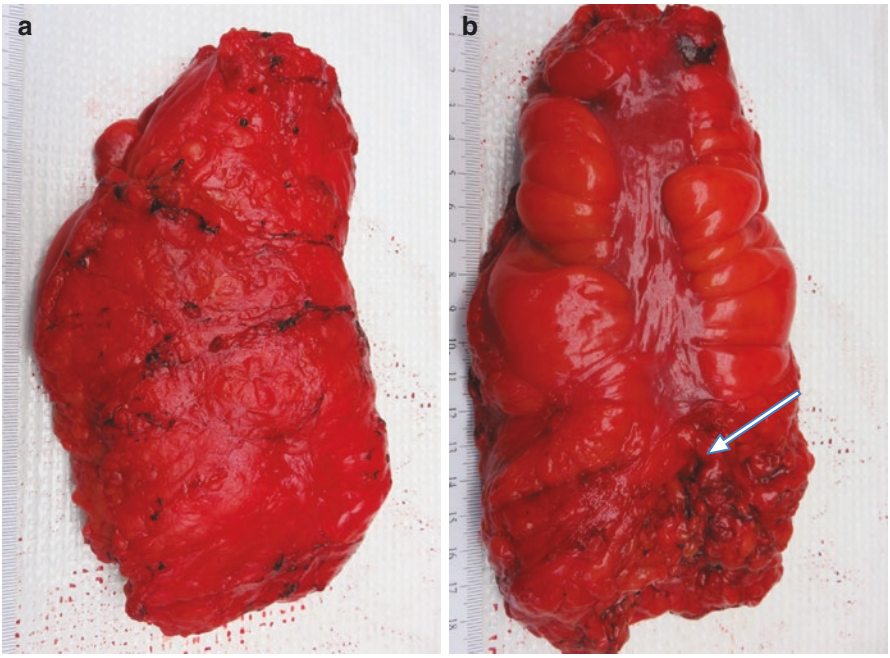


Fig. 5.2 (**a**) Complete mesorectum, posterior aspect, the mesorectal adipose tissue completely wraps the wall of the rectum. (**b**) Incomplete mesorectum, anterior aspect, although there is substantial bulk to the mesorectal envelope, deep defects that expose the muscularis propria are noted

to an inadequate distal margin of resection. For this reason, he proposed that curative rectal cancer surgery could only be achieved by removal of the sphincter complex. This belief spanned most of the first half of the last century. During that time, the distal resection margin was considered to be the only critical margin. This conjecture originated in the fact that cancerous cells distal to the primary mass were a frequent occurrence. This phenomenon is known as "distal tumor spread" (Fig. 5.3) and was first described in 1910 by Cole who identified nests of malignant cells extending up to 4 cm from the distal edge of the primary tumor [14]. The concept gave rise to the "5 cm" rule of distal clearance which held sway [15]. Several subsequent studies published in the 1950s demonstrated that, in actuality, the presence of tumor distal spread beyond 2 cm is a rare event. An important consideration is that in the majority of cases displaying far reaching distal tumor spread, other features of poor prognosis are exhibited, including vascular and perineural invasion as well as lymph node metastasis [16–18]. Subsequent to this realization, distal margins of 2 cm became generally accepted [19, 20]. More recently, with the introduction of surgical techniques such as double stapled anastomosis, as well as the more widespread use of neoadjuvant chemoradiation therapy and the standardization of the TME procedure, 1 cm or even sub-centimeter distal margins have gained greater acceptance [21].

How should we measure the distal margin of resection? And further, who should be doing the measuring? The surgeon of the pathologist? Moreover, should the mea-

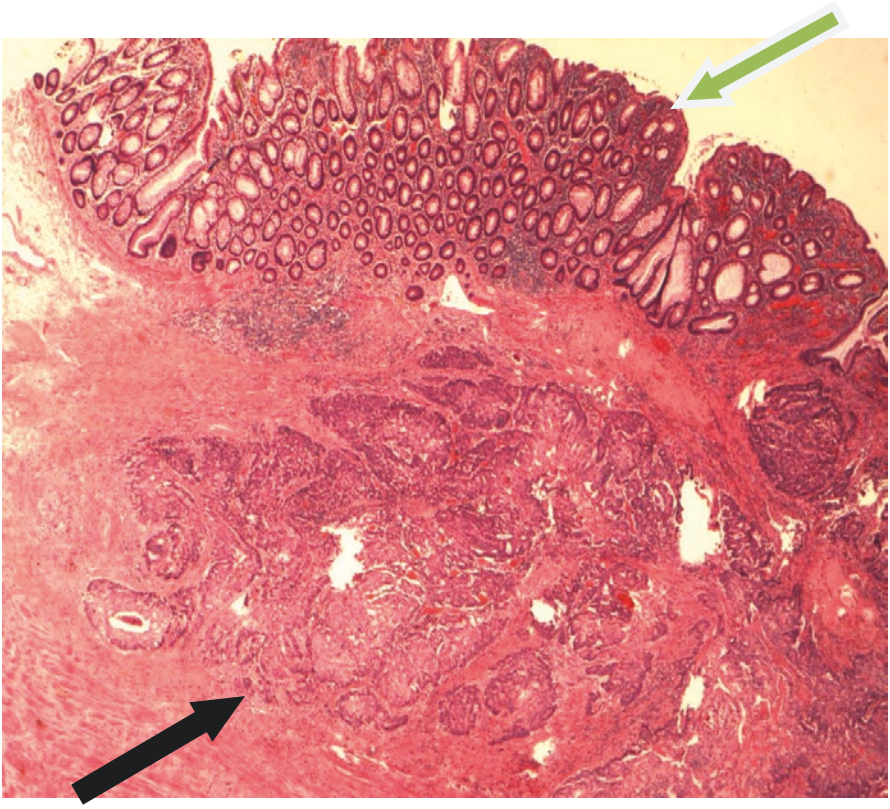


Fig. 5.3 Histological section of an hematoxyilin and eosin stain reveals a focus of discontinuous intramural tumor spread represented by malignant cells extending beyond the main tumor mass (black arrow). Note the benign mucosa overlying the tumor (green arrow)

surements be made *in vivo* or *ex vivo*? And should they be made on the fresh specimen or following formalin fixation? One could argue that the distal margin is better assessed *in vivo* in order to avoid the soft-tissue retraction that normally ensues after resection; an effect which could potentially cause a false decrease in the distance between the tumor and the resection margin [22]. Although the latter occurrence has been described in a few publications, the actual practical influence of this phenomenon is probably minimal [23]. Accurate evaluation of the distal margin is one of the common reasons offered by surgeons to justify the opening of the specimen in the operating room. Although this might be understandable, it is strongly advised, that if there is doubt that an intra-operative consultation is requested. Improper opening of the specimen through the tumor may result in retraction of the mesorectum which will then be difficult to evaluate as will be the circumferential margin of resection. Furthermore, the integrity of the mesorectum should be determined by the pathologist on an unopened specimen where the surface of the resection can be visualized in its entirety. Importantly, prior to any sectioning, the radial margin of resection needs to

be marked with ink, allowing for an accurate measurement on histology. Only after the aforementioned measures are taken should the surgical specimen be partially opened when the intention is to evaluate the distal resection margin specifically. For situations in which the tumor is very close to the distal margin, it is advisable to obtain perpendicular sections so as to include the tumor and the distal margin in one representative slide (Figs. 5.4 and 5.5). This technique will allow a more exact estimation of the distance between the tumor and the distal margin**.**

Circumferential Margin

It is important to remember that rectal cancer used to be associated with a worse prognosis when compared with colon cancer and that principally only obtaining ample distal margins did not significantly decrease the incidence of pelvic

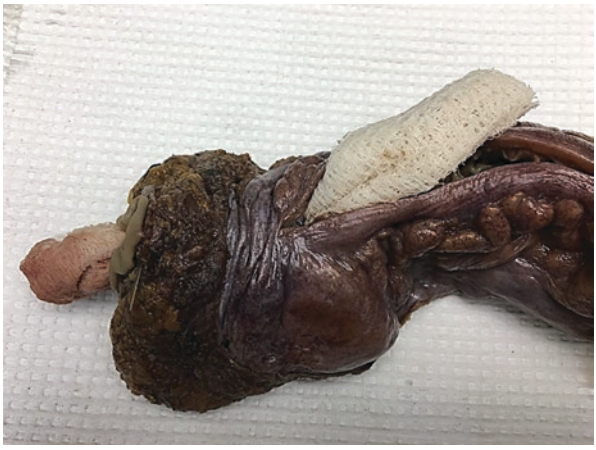


Fig. 5.4 The specimen is opened above and below the tumor and formalin-soaked gauze is introduced to obtain better fixation. This will allow for complete and thin coronal sections that will contain the tumor and surrounding mesorectum

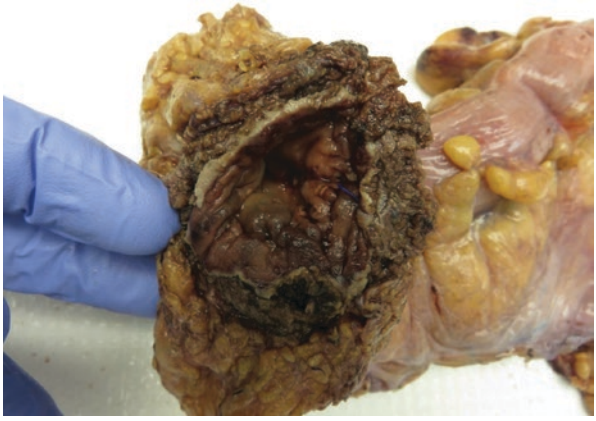


Fig. 5.5 In cases in which the tumor is close to the distal margin, perpendicular sections including the edge of the tumor and the distal margin in the same section allow a more accurate measurement

recurrences. In a landmark study published in 1986, Quirke et al. [24] were able to correlate the high incidence of local recurrence in patients with rectal cancer with the involvement of the circumferential (radial) margin of resection (CRM) rather than with the distal resection margin (Fig. 5.6). This finding was later supported by numerous studies where it has become evident that the presence of tumor ≤ 1 mm from the CRM is not only associated with local recurrence but also with distant metastasis [25–28]. Considering the influence of this parameter in the prognosis of patients with rectal cancer, it is of utmost importance that the pathologist is familiar and proficient with determining its status. Ideally, after recording the objective grading of the mesorectum and after careful palpation along the mesorectal surface to locate the tumoral mass, the entire soft-tissue surrounding the tumor should be ink marked. The purpose of this step is to readily recognize the CRM under the microscope. Although the processing of rectal cancer specimens varies between institutions, it is recommended to follow a specific protocol that will allow a radiology-pathology correlation. Typically the specimen is partially opened caudally and distally, leaving the tumor area itself unopened (Fig. 5.4). Adequate formalin fixation for at least 24 h will allow thin coronal sections (approximately 5 mm in thickness) that should include the tumor and the underlying mesorectum (Fig. 5.7). The number of histological sections varies according to the tumor volume and in also those cases where the patient has received preoperative chemoradiotherapy and where the intention is to assess the gross response of the tumor to treatment (tumor regression grade).

For large tumors, 3–5 sections including the area of the tumor closest to the CRM are usually sufficient. It is important to point out that the distance between the tumor and the CRM should be measured histologically in all cases. In this respect, on histology, involvement of the CRM is the result of 3 specific scenarios; namely:

1. Direct tumor extension
2. A focus of vascular/perineural invasion or tumor deposit and
3. A positive lymph node

Although there are currently no published series addressing the prognostic significance of each of these events, it would be intuitive that direct extension of the tumor into the CRM should carry a more ominous prognosis. In the era of neoadjuvant chemoradiotherapy, marked tumor response can lead to gross disappearance of the neoplasm with only an ulcer or a focus of fibrosis identified in the surgical specimen. In these cases, it is critical to submit the entire area for histological examination so as to capture any potential residual malignant cells and determine their association with the CRM. This approach requires considerable diligence in the era of "watch and wait" management when there has been a complete gross response by the tumor to neoadjuvant therapy. The likelihood of encountering a positive CRM increases with large and deep tumors, those with vascular and perineural invasion, cases of poor tumor differentiation, advanced age and where there are defects in the mesorectal quality [29, 30]. The latter feature has a profound influence on the status of the CRM where logically those specimens with an incomplete peri-tumoral mesorectum are at higher risk of presenting with positive CRMs.

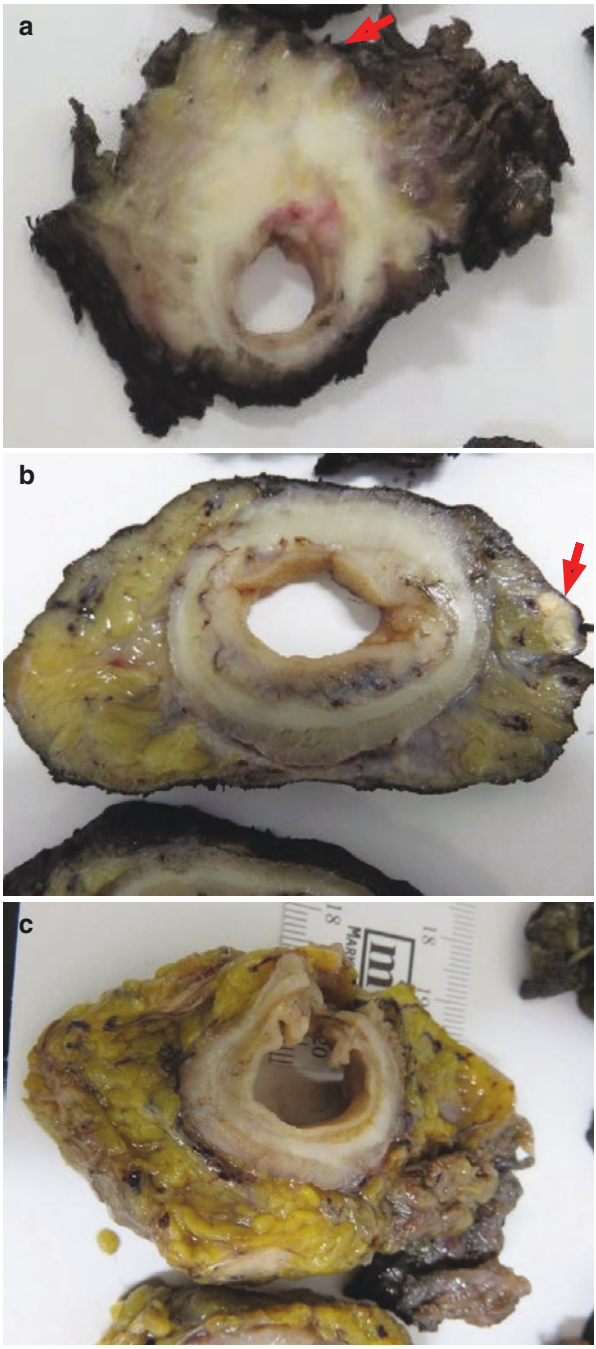


Fig. 5.6 Different patterns of CRM involvement. (**a**) Direct extension of the tumor (arrows). (**b**) Positive node is present at the CRM (arrow). (**c**) discontinuous focus of vascular invasion extends into the CRM (arrow)

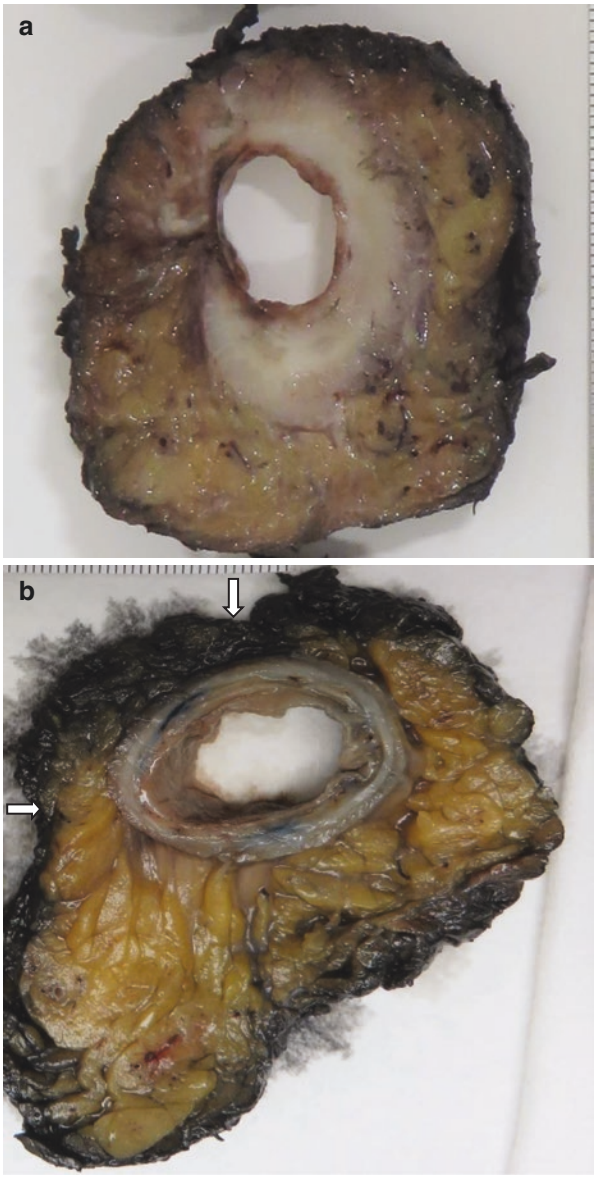
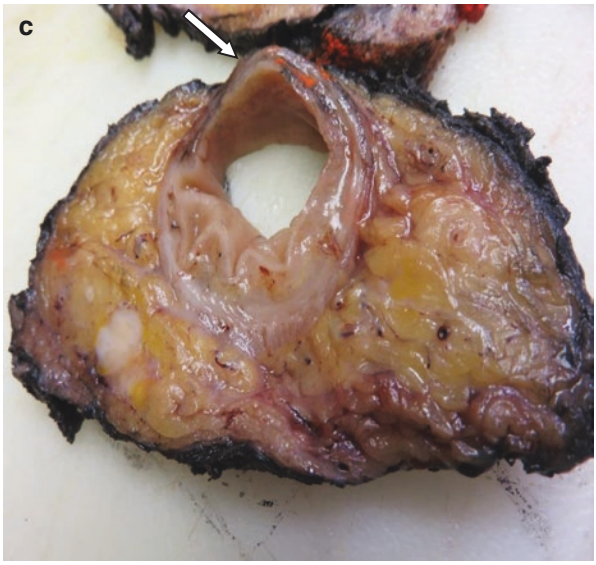


Fig. 5.7 (**a**) Coronal sections of a complete mesorectum shows the wall of the rectum concentrically surrounded by a mesorectal envelope with any defects or tears. (**b**) Cross sections of a near complete mesorectum showing minor defects on the anterior and lateral surfaces that do not expose the muscularis propria (arrows). (**c**) In this coronal section the muscularis propria on the anterior surface is exposed as the result of a large defect (arrow)

Fig. 5.7 (continued)



Lymph Node Evaluation

The number of lymph nodes dissected from colorectal specimens has been shown to correlate with patient outcome, regardless of the positive or negative involvement status [31–34]. This phenomenon appears to be multifactorial and is likely related not only to optimal staging but also to other factors including host age, gender, body habitus and immune response [35–40]. In principle, as the number of nodes retrieved increases so does the chance of the detection of positive nodes. In this regard, given the prognostic effect on survival of positive nodes, then those patients with fewer nodes retrieved are likely to have a worse cancer-specific overall survival. In an ideal world, if the minimum number of nodes required is met within the specimen, the overall hazard risk for death is similar regardless of how many nodes are retrieved. Despite remarkable progress in the field of molecular pathology, pathological stage remains the most important prognostic factor in rectal cancer. In addition lymph node status influences the post-surgical therapeutic decision-making. As the majority of patients with positive lymph nodes will be offered adjuvant chemotherapy, it is then critical that optimal lymph node dissection is carried out by the pathologist. It is important to point out that the rectum inherently contains fewer and smaller lymph nodes when compared with other segments of the intestinal tract [36].

It has been suggested that the number of lymph nodes detected in surgical specimens of rectal cancer reflects the quality of the surgery performed [35] as well as the diligence and effort of the dissecting pathologist. In those cases where there has been an optimal TME, the lymph node harvest depends entirely upon meticulous pathology work, however, in rectal cancer specimens where there is an incomplete

mesorectum, the number of nodes will be logically decreased somewhat regardless of the quality of the work by the pathologist. Currently, the number of lymph nodes considered as "optimal" has been set at 12. In the United States, respected medical organizations such as the American College of Surgeons and the College of American Pathologists have adopted this rather unpopular metric. The establishment of a fixed number of lymph nodes as a reflection of an adequate lymph node dissection has, not surprisingly, created enormous controversy. Furthermore, in rectal cancer patients treated with neoadjuvant therapy, there may be cases in which the number of harvested nodes would be well below this target. In this regard, it has been widely shown that radiation leads to a significant decrease in the number of retrievable mesorectal lymph nodes [41–44], although the relevance of this finding remains unclear. Whilst some studies have suggested that a low number of dissected nodes in rectal cancer specimens following preoperative radiation does not adversely impact patient outcomes, [45, 46] other authors have found a correlation between lymph node harvest post neoadjuvant radiation and survival [47]. A recent meta-analysis and systematic review of 31 articles addressing the number and status of mesorectal lymph nodes in patients with and without neoadjuvant chemoradiation, demonstrated that pre-operative chemoradiation resulted in a mean reduction of 3.9 lymph nodes as well as an average reduction of 0.7 in harvested positive lymph nodes [48]. Individuals who received neoadjuvant radiation only had, on average, 2.1 lymph node less (95% CI 1.7–2.5) resected compared with their counterparts who received no neoadjuvant treatment, show in review of six studies.

Classically, lymph node dissection from rectal cancer specimens is carried out by a combination of palpation and visualization of the mesorectal tissue. This technique results in disparate results as reflected by the extreme variability in lymph node yield noted amongst different centers around the world. In an attempt to increase lymph node harvest from colorectal specimens, several ancillary techniques have been developed. The majority of these are based upon dissolution of the mesenteric/mesorectal fat, a process known as "fat clearing". However, many of the solutions applied for this purpose contain xylene and other chemicals such as acetone, which have been proven to be highly toxic to the operator. Moreover, the majority of these techniques are relatively cumbersome and time consuming [49–51]. A simple and financially feasible alternative consists of the immersion of the mesorectum in pure alcohol for 24–48 h. This method hardens the fat allowing for ultrathin sectioning, while simultaneously whitening the lymph nodes to permit better nodal identification (Fig. 5.8) [47].

Tumor Response to Neoadjuvant Chemoradiotherapy

Over the last two decades, there has been a widespread use of pre-operative therapy to treat patients with advanced rectal cancer with debate concerning the differing radiation and chemotherapeutic scheduling [52–54]. The tumor response to chemoradiotherapy is reflected in volume reduction as well as with tumor downstaging, either in the pT or pN status or in both. Pathological reports of rectal cancer

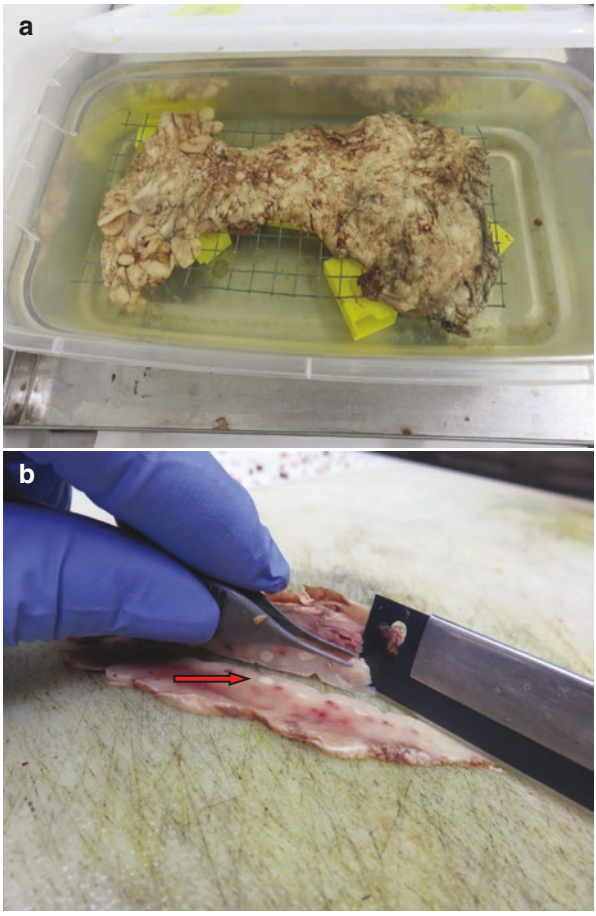


Fig. 5.8 (**a**) Gross picture of the mesorectum after 48 h of alcohol soaking. The adipose tissue becomes firm allowing thin cross sections. (**b**) After fixation in alcohol, the lymphoid tissue is easily recognized in the background of the mesorectal fat (arrows)

specimens following neoadjuvant therapy should always contain the letter "y" preceding the pathological stage (i.e. ypTN) to reflect this effect. Adherence to this nomenclature is critical as it universally communicates that the patient has received pre-operative therapy, even in cases in which the complete clinical history is not available. Tumor response to chemoradiotherapy is variable. Complete pathological response has been reported in up to 25% of cases [55–57]. Although several diagnostic methods have been proposed to evaluate the degree of tumor response to neoadjuvant therapy, it is important to emphasize that a definitive diagnosis of complete response can only be determined through thorough histological examination of the area where the tumor was located. Histological assessment of tumor response is estimated by applying what is known as tumor regression grades. These systems use numerical values that vary according to the degree of tumor volume reduction. The majority of these schemes record the different proportions of residual cancer cells and the surrounding fibrosis and inflammatory reaction and in accordance with which of these components predominates, a definitive number is then assigned (Fig. 5.9).

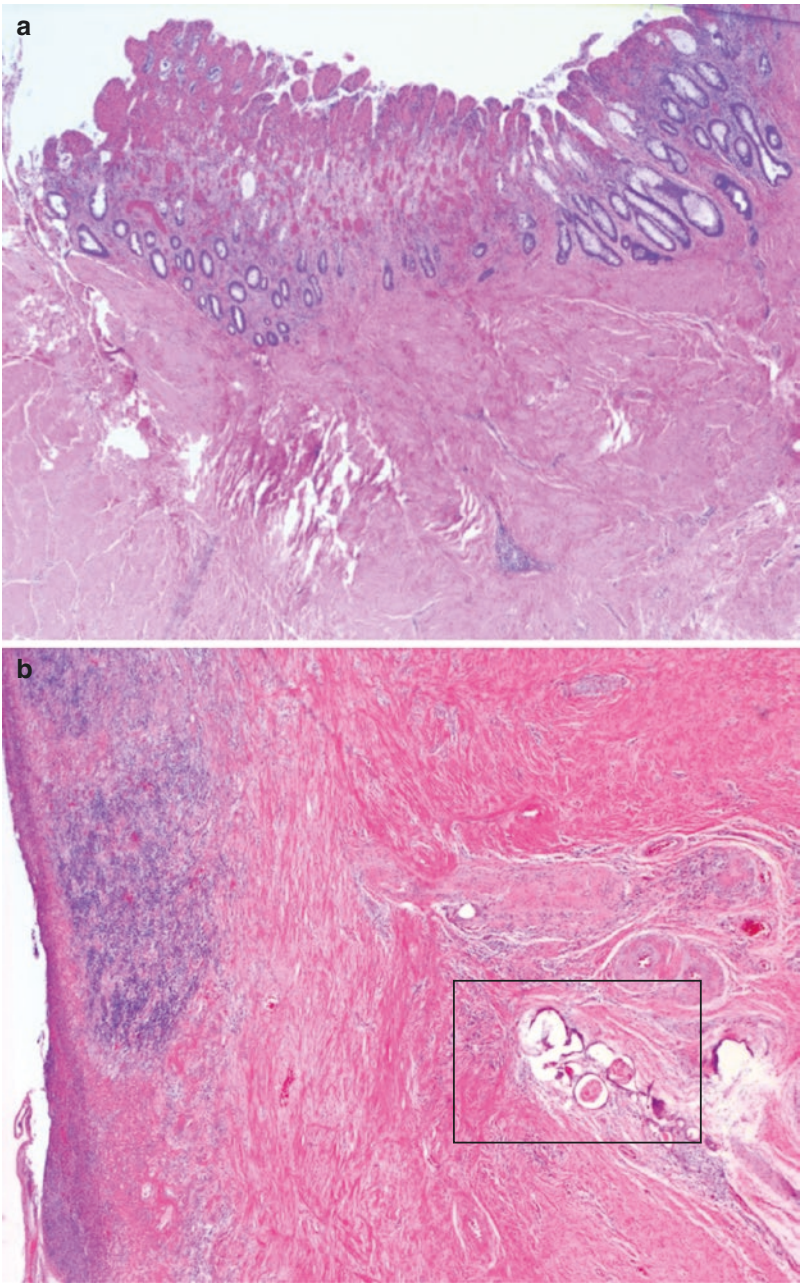


Fig. 5.9 (**a**) Complete pathological response (AJCC/CAP, grade 0) (H&E ×200). (**b**) Near complete response, only a single cluster of malignant glands remains in the specimen after pre-operative chemoradiation (rectangle), (AjCC/CAP grade 1), (H&E ×200). (**c**) Poor tumor response to pre-operative chemoradiation as shown by abundant aggregates of malignant glands, (AJCC/CAP grade 2), (H&E ×200)

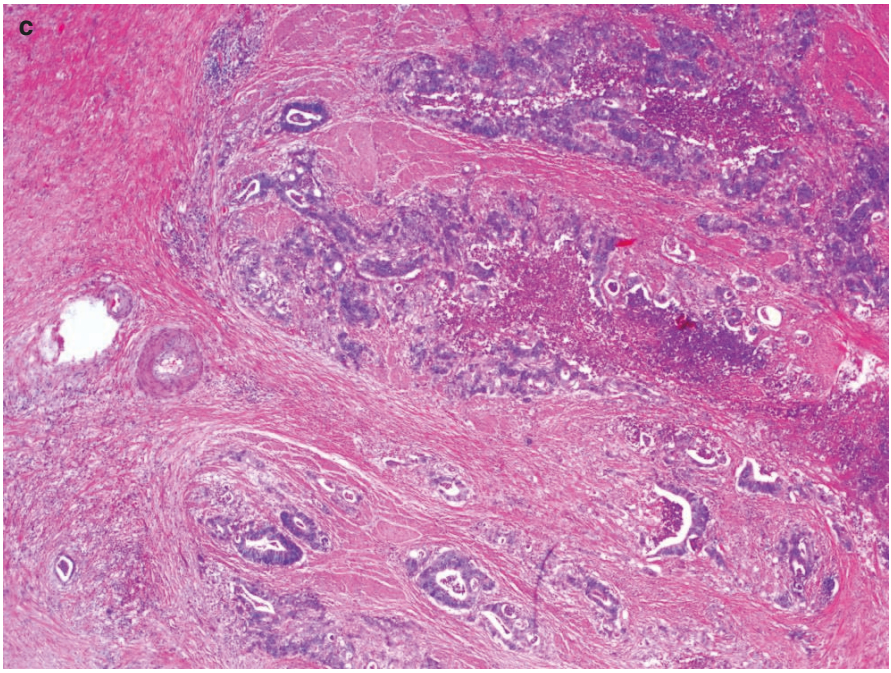


Fig. 5.9 (continued)

The Mandard regression grade system [58] was the first to be applied and was translated for use from esophageal cancer specimens (Table 5.1). Subsequently many other systems have been developed with the same goal including the Dworak method [59] which is widely used throughout Europe (Table 5.2). Following the same concept as these original systems, the College of American Pathologists more recently designed a regression grade [60] that has been proven to better correlate with outcomes (Table 5.3). Whereas the other TRG systems determine their scores based upon residual and tumor tissue, the 4-category AJCC/CAP system primarily focuses on scoring residual tumor. A limitation of such systems lies not in the ends of the spectrum of response or no response but rather in agreement concerning the assessment of intermediate groups as well as the general universality of adoption by pathologists of a standard assessment instrument [61, 62]. The other major drawback of these tumor regression classifications lies in the inter- and intra-observer variability amongst pathologists. This is related to the subjective nature attached to estimating the relative quantity of residual tumor and fibrosis. As expected, methods that use only 3 tiers demonstrate a better level of agreement amongst observers when compared with systems using 5 grades [63]. The ultimate relevance, however, of the degree of tumor regression recorded in response to chemoradiation is the impact of this parameter on patient cancer-specific outcome. In this regard, a near complete or a complete pathological response have both been shown to be associated with improved survival [64–67].

Table 5.1 Mandard tumor regression grade [58]

1. Complete regression (= fibrosis without detectable tissue of tumor)
2. Fibrosis with scattered tumor cells
3. Fibrosis and tumor cells with preponderance of fibrosis
4. Fibrosis and tumor cells with preponderance of tumor cells
5. Tissue of tumor without changes of regression

Table 5.2 Dworak tumor regression grade [59]

0. No regression
1. Predominantly tumor with significant fibrosis and/or vasculopathy
2. Predominantly fibrosis with scattered tumor cells (slightly recognizable histologically)
3. Only scattered tumor cells in the space of fibrosis with/without acellular mucin
4. No vital tumor cells detectable

Table 5.3 American Joint Committee on Cancer and College of American Pathologists Regression Grade AJCC/CAP [60]

Grade 0	Complete response – no viable cancer cells
Grade 1	Moderate response – single or small groups of cancer cells
Grade 2	Minimal response – residual cancer outgrown by fibrosis
Grade 3	Poor response – minimal or no tumor kill, extensive residual cancer

Neoadjuvant therapy frequently results in downstaging of the pT stage (the depth of invasion into the rectal wall). It is important, however, to clarify that T downstaging is not equivalent to tumor regression. The former specifically implies a decrease in the depth of tumoral invasion into the rectal wall, whereas the latter reflects a reduction in tumor volume. Concerning this point, significant tumor regression will often result in rare tumor cells still being identified within the mesorectal tissue (ypT3) without a modification of the tumor stage. Conversely, occasionally downstaging may occur from the pre-operative imaging staging (T3 to ypT2) without a marked decrease in tumor volume. The only circumstance in which tumor regression grades are analogous is when a complete pathological response is achieved, as disappearance of the tumor leads to declaration of a stage ypT0. Neoadjuvant CRT often leads to a discordance between the clinical (cPT) and the pathological stage (ypTN) and this poses the dilemma concerning which stage should be used in order to formulate the postoperative therapeutic plans. This questions the value of the TN staging system in cases where patients have received CRT.

Although the prognostic power of ypT (the depth of tumor invasion into the rectal wall) remains controversial, several studies have clearly shown that the presence of lymph node metastasis post-CRT portends an adverse prognosis. Furthermore, patients with positive nodes following neoadjuvant CRT fare worse than do patients with metastatic lymph nodes who have not received prior therapy. It is important to point out that the degree of tumor regression inversely correlates with the number of

dissected lymph nodes. As previously mentioned, the relationship between the number of lymph nodes harvested and prognosis in patients who received neoadjuvant CRT for rectal cancer remains unclear [35, 40, 44].

Microscopic Evaluation

The pathology report should point out not only the parameters used to define the pTN and ypTN, but also other histological findings that play a role in predicting the prognosis and the behavior of colorectal adenocarcinomas. One of these is in the determination of the variant of adenocarcinoma diagnosed since different types are associated with an increased risk of metastasis. For example, 27.6% of patients with a typical adenocarcinoma will develop metastasis whereas those with mucinous or signet ring cell morphology will have a metastasis in 33.9% and 61.2% of cases over time. These latter two variants also tend to metastasize to the peritoneum with the typical adenocarcinoma having more affinity for the liver [68]. It is equally important to determine the degree of differentiation as well as the presence or absence of perineural and vascular invasion [69–71] (Fig. 5.10). Unfortunately, reference to these findings may be

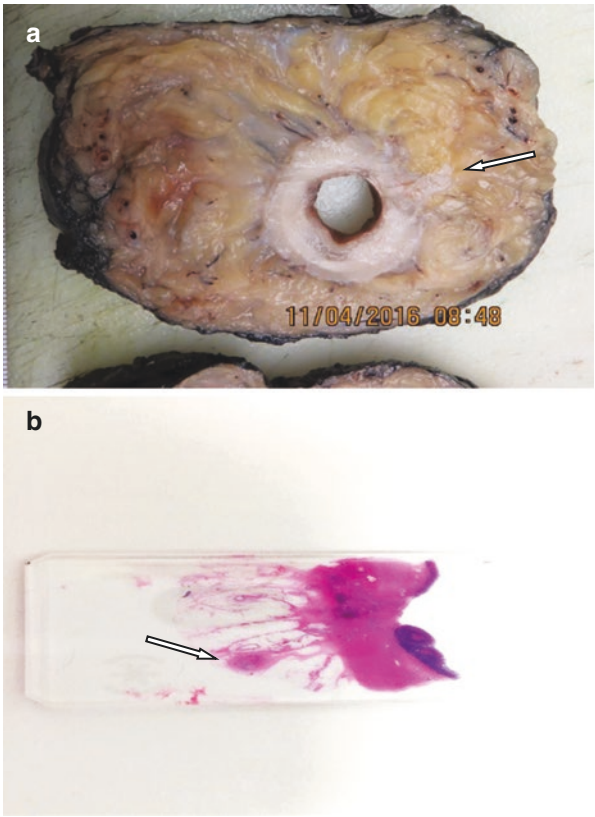


Fig. 5.10 (**a**) Cross section of a rectal cancer specimen showing a focus of extramural vascular invasion (arrow). (**b**) Scanning magnification of a hematoxilyn and eosin stain shows a vein outside the rectal wall filled by a tumor thrombus (arrow)

absent in up to 50% of pathology reports, however, the routine application of synoptic tumor summaries by pathologists at institutions where these have been used have shown an improvement in the quality of the reports [72, 73]. Even though synoptic reports are perceived by clinicians as better and more complete than narrative reports [72] the judgment of the histological findings may be subject to inter- and intra-observer variability hampering the overall accuracy of pathology reporting [74, 75].

Another histological feature that is being increasingly emphasized is the presence of "tumor budding," referring to the presence of individual carcinoma cells or small clusters of tumor cells coming-off the growth front of the main tumor mass (Fig. 5.11). Budding is a negative independent prognostic factor in patients with or without regional lymph metastasis [76–78]. The mechanism of this phenomenon is related to the mesenchymal-epithelial transition and the interaction with the environmental milieu involving complex molecular events controlling the *Wnt* pathway. Phenotypically, budding cells lose their expression of E-cadherin and acquire a mesenchymal characteristic producing and secreting metalloproteinases [79] and other enzymes which degrade the extracellular matrix and which as a consequence allow for the spread of the tumor cells [80]. Unfortunately, this finding may be omitted from the pathology reports or may also be subject to intra- and inter-observer variability. It is conceivable that in the near future tumor budding may be part of the staging system as its documentation, implications and clinical utility become more established.

There is considerable variability related to compliance in reporting of these factors. Although the depth of tumor invasion into the rectal wall and the status of the mesorectal lymph nodes is reported relatively consistently, few studies have shown information concerning the reporting of vascular and perineural invasion and even tumor differentiation is lacking in up to 50% of pathology reports. This fact is particular prevalent at institutions in which the pathologists are not gastrointestinal specialists. In this regard, as stated above, it has been shown by Lankshear et al. [72] in Ontario that the introduction of standardized synoptic pathology reviews which specifically mention each prognostic histopathological parameter in a separate and distinct field has significantly improved the quality of the reporting and the satisfaction of receiving clinicians (oncologists and pathologists). It is important to emphasize that a complete pathological report is not equivalent to an accurate pathological report. The majority of the aforementioned histopathological prognostic indicators suffer from both intra- and inter-observer variability, which diminishes their clinical value [73]. Nevertheless, it is imperative that pathologists worldwide make a concerted effort to become as familiar with and as proficient as possible in recognizing and reporting these important primary pathology elements.

Biologic and Molecular Markers in Colorectal Adenocarcinoma

The morphology and the staging of colorectal adenocarcinomas are not the whole story defining tumor behavior of therapeutic responsiveness. Knowledge obtained from the molecular biology of colorectal adenocarcinomas has expanded the

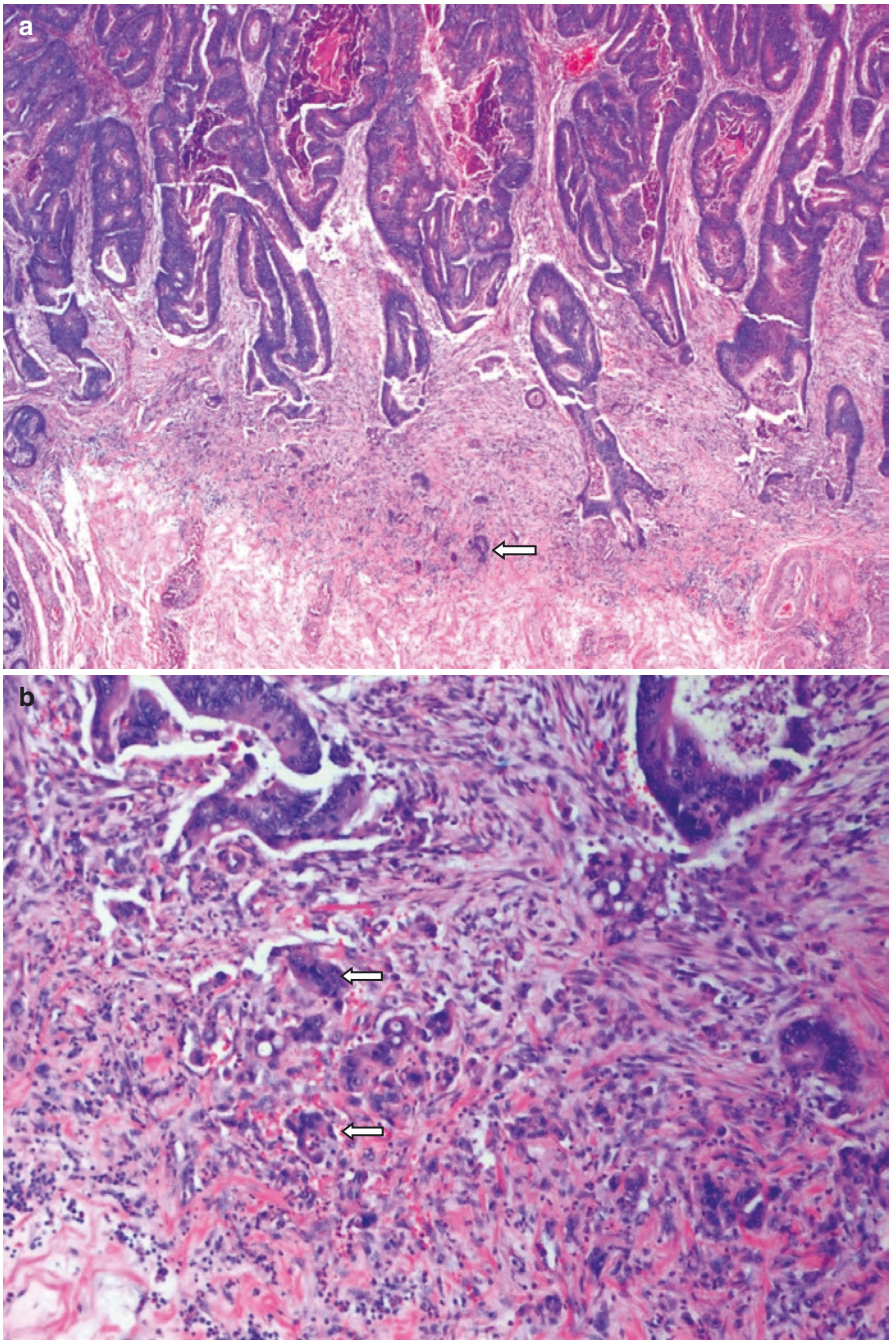


Fig. 5.11 (**a**) Example of "budding" effect. Small clusters of malignant cells are seen at the growing edge of the tumor (arrows), (H&E ×1000). (**b**) Higher power demonstrates in more detail the small nests and isolated malignant cells infiltrating the stroma at the tumor border (arrows), (H&E ×2000)

therapeutic approach. In this respect, there are three molecular pathways in the development of colorectal carcinoma. These include (1) Chromosomal instability, (2) DNA methylation [CpG island methylator phenotype (CIMP]) and (3). Microsatellite instability (MSI).

These systems are not mutually exclusive as a carcinoma may exhibit aberrations of multiple pathways [80, 81]. In the first pathway of chromosomal instability, the carcinomas arise due to an accumulation of chromosomal abnormalities including gains, losses and translocations in oncogenes and tumor suppressor genes that lead to aneuploidy. Aneuploidy is associated with approximately 70% of colorectal carcinomas and is implicated in the traditional adenoma-carcinoma sequence. Tumors that arise through this molecular route are more likely to display KRAS mutations and are more commonly located on the left side of the intestinal tract.

In the second mechanism, carcinomas result from aberrations within specific genes after the DNA duplication is completed. These are referred to as epigenetic changes, largely through methylation of certain genes such as MLH1, CDKN2A, p16 and MGMT. These are events which occur specifically in tumor suppressor genes. In daily practice, MLH1 testing is the most frequently utilized and when there is a defective MLH1 this is secondary to gene hypermethylation. This defective mismatch repair occurs mostly in sporadic carcinomas, with some of these cases related to Lynch syndrome. Such tumors will frequently demonstrate BRAF mutations and CpG island methylation. This CIM phenotype (CIMP) is particularly associated with recurrence following resection of stage III carcinomas of the proximal colon [81] and carries a poor prognosis with a resistance to 5-FU therapy.

The third pathway is based on the fact that DNA nucleotide microsatellite mismatches that occur during DNA duplication are repaired mainly by the genes MSH2, MSH6, MLH1 and PMS2 [82]. Mutations or epigenetic hypermethylation of these genes lead to abnormal proteins that produce microsatellite unstable/high tumors (MSI-H). MSI-H is observed in 15–20% of colorectal carcinomas, but most are sporadic and only 5% are seen in Lynch syndrome. It has long been known that hypermethylated colon cancers tend to occur in the right side of the colon and often display mucinous features as well as poor differentiation. Therefore, rectal cancer with MSI-H is not a common occurrence.

Molecular Testing

A recent consensus that gathered input from key pathology, oncology and molecular societies recommends the performance of testing for biomarkers that have clear prognostic value; most notably, BRAF and MMR along with KRAS and NRAS, which have both shown strong correlation as negative predictors to anti-EGFR therapy response [83]. Depending upon the institutionally-based accepted practices, it is expected that the pathologist will initiate testing in a timely fashion. Accordingly, the first line of molecular testing is usually the detection of mismatch repair protein (MMR) deficiency in carcinoma cells. This is an easy test to perform on formalin-fixed paraffin-embedded tissue using immunohistochemistry (IHC).

This will document the expression or the absence of MLH1, MSH2, MSH6 and PMS2. The tendency here is to perform IHC in all cases of colorectal carcinomas regardless of the patient age not only as a screening tool for possible cases of Lynch syndrome, but also as a prognostic marker and to help oncologists as they face a variety of clinical decisions. These might include whether or not to administer post-operative adjuvant therapy or might influence decision-making concerning the management of advanced disease. Universal testing is generally recommended because of these different goals [83]. MSI testing can also be performed readily with PCR methodology and both techniques (IHC and PCR) show similar sensitivity and specificity, [84] however, immunostaining is much cheaper and has a much faster turn-around time.

About 20% of patients have defects or mutations in one of the DNA repair genes. In about a quarter of those patients, the mutation is based in their germline; the underlying mechanism implicated in Lynch syndrome. Most of the defects are found in the MLH1 protein, but this finding is usually associated with sporadic carcinomas and a mutation for BRAF. The latter mutation essentially rules out familial cases. Recently, this has been shown to be an incrementally cost effective approach for Lynch screening using a combination of IHC, BRAF V600E and MLH1 promoter methylation testing [85]. Loss of the expression of any of the other 3 proteins is associated with Lynch syndrome and will direct further work-up for confirmation [84].

In either group of patients, (Lynch or the sporadic colorectal carcinomas), MMR mutations carry prognostic information. Those with a deficiency typically have a better outcome, regardless of the stage of their disease to the point that in a subset of stage II patients with an MMR defect, the use of postoperative adjuvant therapy may be avoided. Moreover, in more advanced cases, these patients will also not benefit from 5-fluorouracil adjuvant chemotherapy [86–88]. In addition, the value of the MSI-high marker in patients with advanced disease is that it predicts the response to immunotherapy with immune checkpoint-inhibiting drugs, specifically pembrolizumab [89].

Activation of epidermal growth factor receptors (EGFR) on the surface of the carcinoma cells triggers a cascade of signals and alters the role of KRAS, regulating cellular proliferation, angiogenesis and invasive/metastatic capabilities. Mutations in the KRAS gene result in permanent activation of the intracellular signals in the RAS/MAPK pathway. The mutations occur early in carcinogenesis and are observed in 20–50% of cases and when present patients will not benefit from anti-EGFR therapy. In this group the disease-free period tends to be short [89, 90].

Testing for NRAS mutations is thus advisable in order to identify patients who will not benefit from anti-EGFR therapy and it has been suggested that the use of TKIs in patients with RAS- mutated tumors may be detrimental [90]. The testing for KRAS and NRAS mutations can be performed on formalin-fixed paraffin-embedded tissues using PCR or next-generation sequencing techniques. BRAF gene mutations such as V600E transform the protein into its active form, leading to a constant activation of the MEK pathway independent of KRAS. The mutation may partly explain why 60% of patients with wild KRAS are unresponsive to anti-EGFR therapy, hence the importance of testing for BRAF mutation. BRAF mutations are consistently

associated with poor outcomes in patients with metastatic CRC, including those who relapse after adjuvant therapy [89–91]. The combined information rendered by MSI and BRAF testing may be more crucial than conventional staging, identifying specific prognostic subgroups and directing therapy. For patients with high levels of microsatellite instability and BRAF mutation the prognosis is more favorable. By contrast, patients with microsatellite stable or MSI-low tumors and BRAF mutation generally present with more advanced disease, displaying a far worse outcome even in stages I-II as well as seeming chemotherapeutic resistance.

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Part IV
The Surgical Approach

Chapter 6
An Overview of the Tailored Surgical Approach to Rectal Cancer

Michael A. Valente and Tracy L. Hull

Introduction

The approach to the patient with rectal cancer should be conducted in a systematic and manner which will ensure that the proper histological diagnosis, staging, and subsequent treatment modalities are performed with the highest standards. Surgical treatment of rectal cancer should be performed by surgeons in centers with special knowledge, training, and experience in the multidisciplinary treatment of these tumors. Treatment of adenocarcinoma of the rectum has undergone a major change over the last 20 years, one that has been seldom seen in other solid tumors. The surgeon plays an integral part of the multidisciplinary team, and his or her role represents a prognostic factor for the successful treatment of this disease. This chapter focuses on an overview of how these patients are approached from a surgical standpoint and what criteria are used to decide which operation or treatment is best for each specific patient.

The key components of how to evaluate any patient with rectal cancer begins with the fundamental principles of a detailed personal and family history, physical examination, histological confirmation of the tumor and a full colonoscopy. Essential elements in the multidisciplinary workup of rectal cancer include the following:

- Patients age and medical comorbidities (physiological age; ability to undergo abdominopelvic surgery and/or receive chemoradiotherapy)
- Tumor location
- Tumor stage (TNM classification)

M. A. Valente (✉) · T. L. Hull
Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA
e-mail: VALENTM2@ccf.org

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- Anal sphincter status (location of tumor and physiological function of sphincters)
- Obstetrical history in women
- Previous anal or pelvic surgery
- History of radiation treatment
- Patient's wishes/expectations
- Surgeon experience and skill

Diagnosis and Staging of Rectal Cancer

Accurate diagnosis and staging of rectal cancer is of the utmost importance in order to make a sound multidisciplinary decision for the tailored surgical treatment. Tumor location with respect to the anorectal ring (puborectalis sling, anorectal junction), anal verge and peritoneal reflection, TNM staging, and circumferential resection margins all need to be evaluated before treatment can begin. There exist several different imaging modalities that are suitable for rectal cancer staging, tumor location, and restaging after treatment, but not all of them have the same accuracy for each indication [1].

Multidisciplinary team approach is strongly recommended on all rectal cancer cases. It is compulsory at our institution that every rectal cancer case, regardless of clinical stage, is discussed with the multidisciplinary team, which consists of: medical oncology, radiation oncology, gastrointestinal pathology, gastrointestinal radiology, colorectal surgeons, liver/thoracic surgeons, genetic counselors, and the other members of the nursing support staff.

All of the information gathered before treatment begins must then be assimilated in a fashion that treats the particular patient. Treatment is built upon accurate staging, but tailored to each individual patient, based upon their age, physiological status, functional status, and a thorough understanding by the patient of the various treatment options that exist.

Tumor Location Evaluation

Low vs Middle vs High Rectal Tumors

A combination of both a digital rectal examination (DRE) and rigid proctoscopy is the most accurate method for localizing rectal tumors, especially in the low and mid-level of the rectum. Flexible endoscopy may not provide an exact localization of rectal tumors due to its unreliability and inaccuracy. In both DRE and endoscopy, the anal verge is the anatomical landmark that is used as a reference point for accurate measurement. All rectal tumors should be categorized according to their most distal edge measured from the anal verge. Typically, any tumor that has its distal

edge 15 cm or less from the anal verge can be considered a rectal cancer [2]. Additionally, the tumor should be categorized as anterior, posterior, and right or left on rigid proctoscopy and on DRE the tumor should be characterized as mobile, tethered, or fixed, which corresponds to depth of invasion through the rectal wall. Localization is absolutely mandatory for surgical decision-making and to help determine if sphincter-preservation is feasible. When determining if sphincter-preservation can be accomplished, the examiner must assess the tumor's lower edge in relationship to the anorectal ring. Tumors that sit below the anorectal ring, for the most part, cannot undergo intestinal continuity with an oncologically sound procedure. It should be noted that DRE and proctoscopy may be inaccurate based on the experience of the person performing the examination. While these methods are highly reproducible for defining the level of the tumor, considerable variation in pelvic anatomy exists between patients. This fact is especially true in regards to the length of the anal canal (women have a shorter anal canal than men) and the distance between the pelvic floor and the anterior peritoneal reflection [3]. Based on these anatomical differences, body habitus and gender must be taken into consideration in the final assessment of the location of the tumor [2].

In conjunction with the physical examination, the use of magnetic resonance imaging (MRI) has been shown to be accurate in both measuring the distance of the tumor to the anorectal ring and the overall length of the tumor [4, 5]. In terms of identifying the extraperitoneal versus the intraperitoneal rectum, there exists some controversy in the exact localization of rectal tumors even when the peritoneal reflection is visualized on MRI. This is important to mention because by definition, tumors that sit at or above the peritoneal reflection should be treated like distal colon carcinoma, and should, in the vast majority of instances, *not* receive neoadjuvant or adjuvant radio(chemo) therapy.

Tumor Staging

T Stage

Clinical staging with endorectal ultrasound (EUS) and/or by dedicated high resolution rectal magnetic resonance imaging (MRI) should be performed on all mid and distal tumors and select upper tumors. There are advantages and disadvantages to both modalities and therefore can be considered complementary to each other. EUS is considered more accurate for distinguishing between T1 and T2 lesions over MRI. EUS, however, is not well suited for high tumors and/or bulky tumors (T4). Additionally, stenotic tumors pose a technical problem, as the ultrasound probe may not be able to traverse the lesion for accurate staging.

In distinguishing between T2 versus T3 rectal cancers, MRI seems to be more accurate, although EUS and MRI have the same limitations in distinguishing between borderline T2 and T3 lesions. Over staging of T2 lesions is caused, in part, by potential desmoplastic reaction of the peritumoral tissues. On the other hand, T3

lesions are well distinguishable from T4 lesions with the aid of MRI. The accurate diagnosis of T3 from T2 lesions is important, as T3 lesions of the mid and low rectum should receive neoadjuvant chemoradiation in most instances. In our experience, ultrasound may be better when looking anteriorly (invasion into prostate/bladder or vagina) and MRI is better for evaluating the circumferential margin.

Circumferential Resection Margin/Mesorectal Fascia Involvement

The circumferential resection margin (CRM) is used to describe the extent of the embryological plane that posteriorly and somewhat laterally envelops the mesentery, fat, and lymph nodes of the rectum. It can be further defined as the shortest distance between the rectal tumor and the mesorectal fascia, which corresponds to the plane that is traditionally described in total mesorectal excision (TME) [2]. Mesorectal fascia (MRF) involvement is the typical terminology when describing imaging, most often on MRI, where the tumor extends to this embryological plane. In terms of preoperative features, the relationship of the rectal cancer to the CRM/MRF has become one of the most powerful indicators of outcome [6, 7]. Currently, the preoperative staging cut-off for a positive CRM is 1 mm. If the MRF/CRM is positive or $\leq$1 mm on MRI, there is a clear correlation that the final specimen will have a positive CRM if only TME is undertaken. Thus, with the information garnered on MRI, a positive or "threatened" CRM/MRF is important information that may help make the decision to pursue neoadjuvant chemoradiation followed by TME or a more aggressive resection.

N Stage

Accurate lymph node diagnosis continues to be a diagnostic problem on MRI and ultrasound. Size alone is not a good predictor of malignancy, but nodes >8 mm are considered suspicious for harboring malignancy. Morphological features, such as shape, border irregularity, and heterogeneity seem to be better predictors of metastatic disease than size alone. Despite overall low sensitivity and sensitivity (66% and 76%, respectively), MRI is the recommended modality for diagnosis of nodal disease [2].

M Stage

Staging of distant metastatic lesions is performed with CT scans of the chest, abdomen and pelvis. Dedicated MRI of the liver may be useful for equivocal lesions seen on CT scan. Brain CT and bone scans should be obtained for those with specific

symptoms. Positron emission tomography (PET/CT or PET/MRI) should be used on a case-by-case basis and is not recommended as an initial staging modality, unless suspicious lesions are found on CT or MRI and positivity will alter the surgical plan. The various treatment modalities and the complex decision making process for stage IV disease will be discussed in other sections of this book.

Treatment Strategies and Operative Considerations

The treatment strategies described below are the most commonly performed and have the most data to support their use. There exist several hypothetical but real clinical scenarios in which variations and deviations from the "gold standard" approach exist based on several patient-specific variables including chronological and physiological age, ability to undergo radical surgery, the role of radiation and chemotherapy, anal sphincter function, and patient wishes. Tumor-specific variables play a major role in the type of surgery performed and the ability to preserve the anal sphincters. Subsequent sections of this book will go into more detail on topics discussed here.

Local Excision

Select clinical T1 (sm-1, sm-2) N0M0 rectal cancers can be treated with local excision versus standard TME surgery. Local excision is an appropriate option for early rectal cancer as long as the tumor encompasses less than one third to one half of the bowel lumen, is less than 3–4 cm in dimension and lacks high risk features such as lymphovascular and perineural invasion, poor differentiation, or >sm-2. Local excision can also be considered as definitive treatment for patients with more advanced disease who are medically unfit for radical surgery [2]. Accurate preoperative staging is essential in patient selection for transanal resection. If, after a proper local excision (either via a traditional transanal approach or via transanal endoscopic surgery (TES), the pathology reveals high risk features, sm-3, or T2/3, radical resection with proper total mesorectal excision (TME) should be recommended for the majority of patients. Salvage TME after transanal excision is feasible and safe, but sphincter preservation may be compromised in some patients and long term success may be disappointing [8–11]. If the patient is a poor operative candidate and radical surgery is prohibited or if the patient refuses surgery and/or permanent colostomy (if sphincter preservation is not possible), then chemoradiotherapy should be undertaken [12, 13] and it should be noted that in series with long-term follow up, the pelvic failure rates have been reported as high as 18–25% in this subset of patients [14].

There also exists the potential in select inoperable patients or those that refuse radical surgery with T2/T3 lesions that neoadjuvant 5-FU based chemoradiotherapy is given followed by transanal excision. This approach has been reported in few

series and should be limited to a very small subset of patients with features described above or in the setting of a clinical trial [15]. More in-depth discussions on local treatment are discussed in subsequent chapters.

Standard Excision (TME)

Total mesorectal excision is the operation of choice for the curative resection of cancers of the middle and lower thirds of the rectum, either as part of a low anterior resection (LAR) with sphincter preservation or an abdominal perineal resection (APR). For tumors of the upper third of the rectum, a tumor specific partial mesorectal excision (PME) should be used with the mesorectum divided no less than 5 cm below the lower margin of the tumor [2].

T2N0M0

T2 lesions of the rectum should undergo standard TME without neoadjuvant treatment. The risk of positive lymph nodes ranges from 15% to 20%, so local therapy is not recommended. If, after radical surgery (without neoadjuvant treatment), T3 is found in the specimen (high or mid lesions) observation may be considered; low tumors with either T3, N+ or CRM+, should be discussed with a multidisciplinary team for consideration to giving chemotherapy or chemoradiation adjuvantly. Some very large and bulky T2N0 lesions may to be difficult to obtain an R0 resection (especially in a narrow male pelvis) and consideration may be given to downsizing the tumor with neoadjuvant radiotherapy followed by standard TME.

Locally Advanced Tumors (T3-4Nx or TxN1-2): The Role of Multimodality Therapy

Multimodality therapy has become standard for patients with locally advanced rectal cancers (T3-4Nx or TxN1-2) of the mid and distal rectum, especially if bulky, tethered, or fixed [2]. Initially given postoperatively (adjuvant), chemoradiotherapy demonstrated reduced local recurrence from 55% to 33% with significant disease-free survival in patients with locally advanced disease [2]. Currently, there is overwhelming evidence to give chemoradiotherapy pre-operatively (neoadjuvant) due to greater efficacy, lower toxicity, and better long-term outcomes [2].

For locally advanced tumors of the mid and distal rectum, two possible treatment modalities exist: short course radiotherapy without chemotherapy (5 Gray daily over 5 days) followed by immediate (within 1 week) TME or long course chemoradiotherapy (45–50.4 Gray over 5–6 weeks with concurrent 5-FU chemotherapy) followed by delayed (8–12 weeks) TME. Most often, in North America and in some European countries, combined modality long-course chemoradiother-

apy has become the treatment of choice. The majority of patients receiving long-course therapy will obtain tumor downstaging, in which the final pathological stage at the time of surgery is lower than the initial clinical stage at the time of presentation. Tumor downsizing may help facilitate complete tumor resection and, in the setting of low-lying tumors, may alter the surgical plan by making a sphincter-saving surgery possible [2]. Additionally, as many as 15–20% of patients will have a complete pathological response to treatment in which there are no viable tumor cells detected in the specimen. It is currently the standard of care to give these patients adjuvant chemotherapy post-resection, regardless of final pathological stage.

Short-course radiotherapy is usually reserved for cases in which the tumor margin threatens the MRF and situations where tumor regression and downsizing would not improve resection quality or sphincter preservation, or in situations where the patient could not tolerate long-course therapy. A much more in-depth discussion on chemoradiotherapy is included in subsequent sections of this book.

T3-4, MRF+/CRM+

Locally advanced tumors are those that are defined as extending beyond the rectal wall with infiltration of surrounding organs or structures. Resectability depends on several factors, namely whether or not the surgeon is able to remove all the invading organs with negative margins and whether or not the patient is physiologically fit and able to tolerate the operation and potential morbidity. All patients with T4 resectable cancer should be considered for upfront chemoradiotherapy. The role of intra-operative radiotherapy (IORT) is also a consideration in patients with MRF+/CRM+ preoperatively.

Other Surgical Considerations

Neorectal Reservoir Construction

Low anterior resection syndrome consisting of fecal urgency, frequency, clustering, and fecal incontinence may all occur after TME, in part, due to a loss of rectal reservoir. Anal sphincter damage and physiological changes from radiotherapy may also influence these debilitating symptoms. Various techniques have emerged to help improve post-operative function, such as the colonic J-pouch, transverse coloplasty, and a side-to-end configuration. At our institution, when feasible, we prefer a colonic J-pouch reconstruction. It has been shown in metaanalyses that the colonic J pouch is superior to a straight coloanal anastomosis in terms of reduced bowel frequency and urgency up to 18 months after surgery [16–18]. Transverse coloplasty can still be considered if a pouch or a side-to-end anastomosis cannot be performed.

Fecal Diversion

Diversion of the fecal stream should be strongly considered for all patients undergoing TME for rectal cancer in the mid and low rectum. This is especially true for those patients who received neoadjuvant radiotherapy to the pelvis and those whose colorectal anastomosis is <7 cm from the anal verge. It is routine practice at our institution to strongly consider construction of a loop ileostomy in these situations. After using this approach for several decades, we feel that fecal diversion has substantially mitigated the deleterious and possible lethal effects of pelvic sepsis due to an anastomotic dehiscence and has decreased re-operative rates. Additionally, in a recent metaanalysis of over 11,000 patients, including four randomized controlled trials, the authors found a lower anastomotic leak rate with fecal diversion as well [19]. While a temporary loop ileostomy can lead to significant problems such as dehydration from high output, the septic consequences of a leak can be lethal, particularly in frail, elderly patients. Therefore, even if a patient requires antidiarrheal medication or even intravenous fluid while the temporary stoma is in place, these temporary unwanted issues may be preferable to the consequences of a leak.

Physiological Function of the Anal Sphincters

In the era of increased sphincter-saving operations, the surgeon must evaluate the baseline function of the anal sphincter complex before any surgery is undertaken. Even when technically feasible, an ultra-low anterior resection (with or without neorectal reservoir) or an intersphincteric resection may not be suitable for a patient with weakened or damaged anal sphincters. This fact is especially true for patients with known abnormalities of continence from a variety of causes (namely, obstetrical trauma) or patients with certain comorbid conditions that impeded their neurological function (ie., multiple sclerosis, diabetes). Even patients with marginal sphincters and decreased mobility may have poor quality of life due to the inability to quickly reach the toilet and may be counseled to have a permanent stoma. If there is any uncertainty regarding a patient's anal sphincter status, appropriate physiological and anatomical tests should be obtained, including endoanal ultrasound and anal physiology. Other methods used to test pelvic floor function include the use of porridge enemas to check the ability of the pelvic floor to hold stool [20]. Potential alterations in quality of life, including LAR syndrome and sphincter/pelvic floor muscle dysfunction must be considered when recommending sphincter- preservation surgery. Patients deserve to be fully informed in order to participate in this important decision making process (i.e., permanent stoma versus low anastomosis).

Conclusion

Modern management of rectal cancer has become multidimensional and requires a significant coordinated effort between multiple caregivers. A combination of factors such as a better understanding of the disease process, more accurate radiological staging, multimodality therapeutic intervention, refined surgical technique, and more detailed histopathological reporting have all contributed to improvements in the management and survival of patients with rectal cancer [2]. Patients should be part of the multidisciplinary approach to their care and participate in decision making. Each patient is unique and their treatment plan should be tailored individually to them.

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Chapter 7
Total Mesorectal Excision: Embryology, Anatomy, Technique and Outcomes

Ashish Gupta, Sanjeev Dayal, and Brendan J. Moran

Introduction: Background

The surgery and outcomes for rectal cancer have improved dramatically largely as a consequence of the initial description and subsequent popularization of total mesorectal excision (TME) [1, 2]. The procedure of TME entails the removal of the rectum (surrounded by the mesorectum which is encompassed by the mesorectal fascia) with division of the muscle tube at the level of the anal canal. TME is particularly applicable for what is termed a "low" anterior resection where intestinal continuity is restored by a colo-anal anastomosis. The anastomosis after TME will effectively be within 3–4 cms of the anal verge.

The term anterior resection is by definition only applicable if the superior rectal artery has been ligated and an anastomosis constructed at least to the top of the rectum (Fig. 7.1).

In broad terms, TME is the optimal technique for "operable" rectal cancer but not all patients with rectal cancer either need to undergo, or are suitable for, a "total" mesorectal excision. In this regard, early tumours, perhaps between 5% and 10% of all patients with rectal cancer, can be treated by a local excision alone, particularly using the principles of Transanal Endoscopic Microsurgery (TEM). Details of this approach and its indications and outcome are covered elsewhere in this book. At the other extreme, tumours that breach the mesorectal fascia, or which involve the anal sphincter complex/levator ani muscle require consideration for pre-operative

A. Gupta · S. Dayal · B. J. Moran (✉)
Basingstoke and North Hampshire Hospital, Hampshire Hospitals Foundation Trust, Basingstoke, UK
e-mail: Brendan.Moran@hhft.nhs.uk

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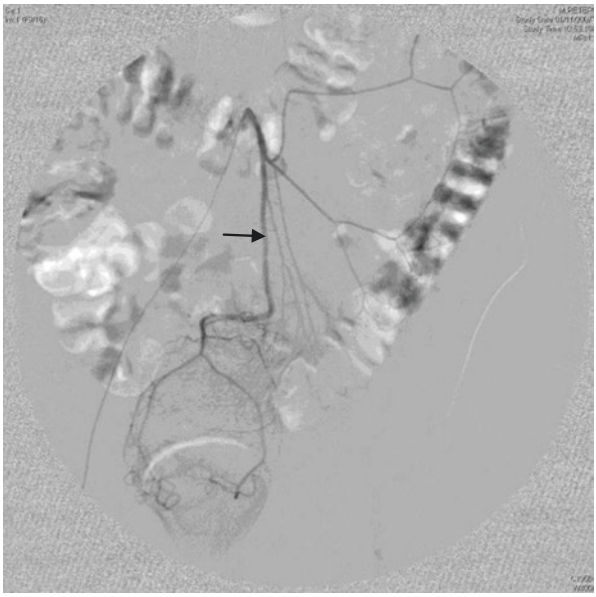

Fig. 7.1 Inferior Mesenteric Angiogram outlining the blood supply to the rectum and left colon. The main vessel continues caudally as the superior rectal (arrow) having given off the left colic and sigmoid branches. (Manual of Total Mesorectal Excision, Moran and Heald, Copyright (2018), reproduced by permission of Taylor & Francis Books UK)

(neoadjuvant therapy). If a low rectal cancer involves the external anal sphincter complex, an abdomino-perineal excision (APE) is required with creation of a permanent stoma. For each patient, the feasibility of a restorative resection ultimately depends upon a number of factors some of which are related to the tumour, or to the patient and to a lesser extent to the surgeon. The main tumour-related factors include the distance of the tumour from the anal verge, its fixity to surrounding tissues and the presence or absence of metastatic disease. Patient-related factors include overall body habitus, the size and depth of the pelvis and both the anal sphincter integrity and its function. Surgeon-dependent factors include the overall surgical experience and training and additionally the availability of suitably experienced surgical assistants and an operating theatre team as well as access to the latest minimally invasive equipment.

The concept of TME for rectal cancer involves what has been described as "circumferential awareness" incorporating circumferential staging, circumferential down-staging, circumferential surgery and circumferential pathology [1]. Circumferential staging incorporates clinical examination and more recently cross-sectional imaging, particularly pelvic CT and MRI (Fig. 7.2) [3, 4].

In advanced tumours, that either involve, or threaten the margins, circumferential down-staging and/or "downsizing" may be achieved by preoperative radiotherapy or chemo-radiotherapy. The concept of circumferential surgery has emanated from the description of total mesorectal excision (TME) popularised by Heald [1, 2] with "specimen orientated surgery" (Fig. 7.3).

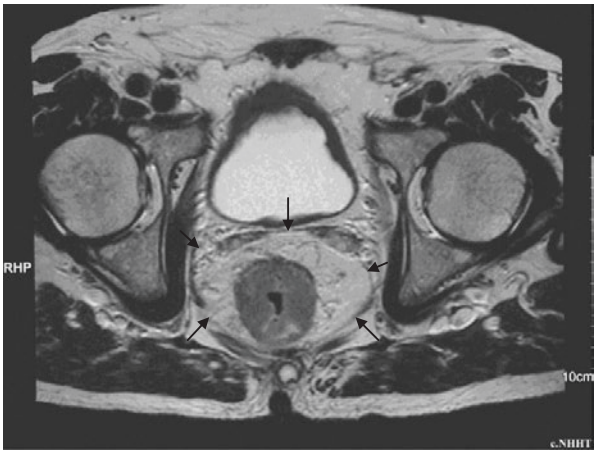

Fig. 7.2 Pelvic MRI showing a circumferential rectal cancer surrounded by the mesorectum encompassed by the mesorectal fascia (arrows). A total mesorectal excision (TME), in the mesorectal fascial plane, will have a clear circumferential resection margin (CRM). The radiological stage is mrT3 with predicted clear CRM

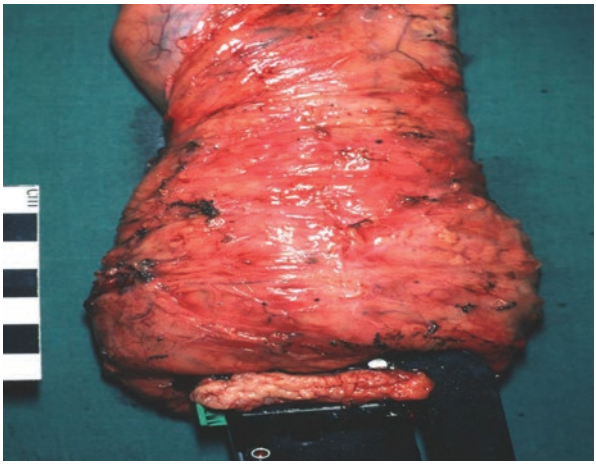

Fig. 7.3 A Total Mesorectal Excision (TME) specimen, illustrating the shiny mesorectal fascia surrounding the fatty mesorectum and sealed at the distal end with a linear stapler as utilized in the "Moran Triple Stapling Technique" [5, 6]

Embryology and Anatomy

During the fourth week of gestation, the embryological gastrointestinal tract divides into three distinct parts, the foregut supplied by the coeliac artery, the midgut vascularised by the superior mesenteric artery and the hindgut supported by the inferior mesenteric artery. The hindgut comprises the distal one-third of the transverse colon with the descending and sigmoid colon, the rectum and the cloaca. The cloaca, which is the common urogenital sinus, later partitions into the anterior urinary and posterior ano-rectal compartments (or triangles). The primitive gut is suspended by a dorsal mesentery containing its relevant blood vessels and lymphatics and although the distal hindgut does not have a true mesentery in the strictest sense, it has a

similar or homologous territory which is its mesorectum. An understanding of detailed mesorectal anatomy plays a pivotal part when performing a TME.

The rectum extends from the sacral promontory to the levator ani muscle and usually measures 15 cm in length. Circumferential longitudinal muscle covering the rectum replaces the three taeniae coli on the colon.

Presacral and Retrorectal Space

Posteriorly, the rectum and its enveloping mesorectum is covered with endopelvic fascia, (also called presacral fascia) which runs in the hollow of the sacrum and which provides protection to the underlying autonomic nerves and the presacral venous plexus. The space between the periosteum of the sacrum and the presacral fascia is the presacral space. Whilst performing posterior mobilization of the rectum it is cautionary to stay in the retrorectal space anterior to the presacral fascia in order to avoid major bleeding and nerve damage. The retrorectal space is limited anteriorly by the mesorectal fascia and posteriorly by presacral (or rectosacral) fascia of Waldeyer [7].

Nerve Supply

The rectum and upper anal canal are supplied by the autonomic nervous system (sympathetic and parasympathetic) which are also responsible for sexual and urinary function, so that their operative recognition and preservation whenever possible whilst performing a TME is vital. Damage to the sympathetic nerves may result in urinary incontinence and impaired ejaculation, whereas parasympathetic nerve damage leads to erectile dysfunction/impotence and urinary bladder dysfunction. Lubrication of the external genital organs in both genders and an inability to experience orgasm in females can also manifest due to nerve injury. Unilateral nerve damage may be compensated by the intact contralateral nervous input in most cases [8, 9]. There are several identifiable points of autonomic nerve injury. The inferior mesenteric and superior hypogastric plexus surround the inferior mesenteric artery for up to 5 cm from its origin from the aorta. A high-tie arterial ligation is thus likely to damage some of the adjacent nerve fibres and a low tie may well be preferred in selected cases so as to avoid nerve injury, since the oncological gain for a high tie in every case can be debated [10, 11]. The superior hypogastric plexus is situated in front of the L5 vertebral body and the sacral promontory and between the two common iliac arteries. It is formed by the union of multiple nerve fibres which descend from the aortic plexus and the lumbar ganglia. Upon entering the pelvis, it divides into right and left superior hypogastric nerves which run at the sides of the rectum [12]. These superior hypogastric nerves are intimately related to the presacral fascia and contain sympathetic fibres from vertebral levels T10-L2. The superior

hypogastric nerves in the pelvis join the inferior hypogastric plexus (also commonly called the pelvic plexus), which is formed by the pelvic splanchnic nerves carrying parasympathetic fibres from S2–4 and which emerge through the sacral foramina behind the presacral fascia (Fig. 7.4).

These pelvic splanchnic nerves are also called erigent nerves or erigent pillars. The upper part of the inferior hypogastric plexus extends along the prostate and seminal vesicles and is separated from the rectum by the rectoprostatic septum (Denonvilliers' fascia). During the anterior mobilization of the rectum, it is preferable to start in the midline directly behind the rectoprostatic septum where the nerve fibre density consistently increases towards the lateral septal sides. The lower part of the inferior hypogastric plexus extends dorsolaterally along the prostate as the neurovascular bundle approaching the apex of the prostate and penetrating the urogenital diaphragm [8].

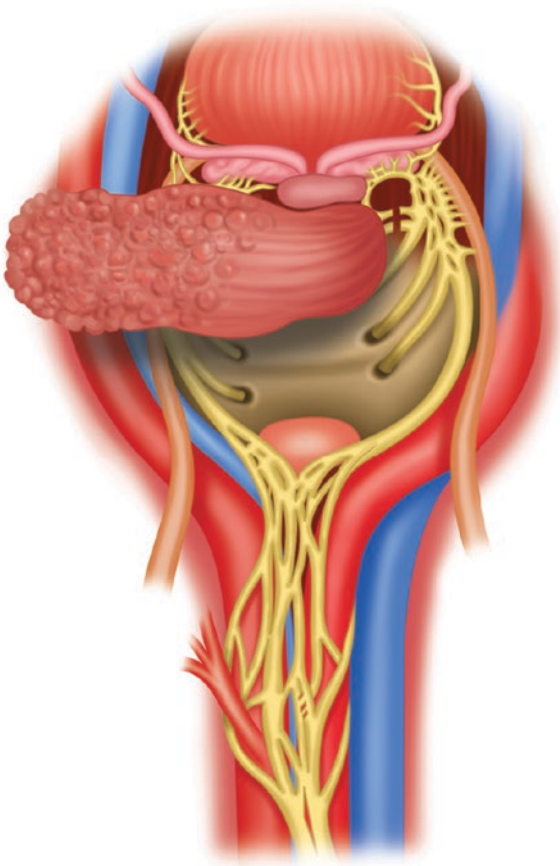

Fig. 7.4 A schematic representation of the pelvic autonomic nerve plexus with the hypogastric nerves arising form the superior hypogastric plexus overlying the anterior surface of the aorta and the aortic bifurcation. The hypogastric nerves are joined by sacral branches, particularly S2, S3, and S4. (Reproduced from [12] with permission from John Wiley and Sons)

Lympho-Vascular Supply of Rectum

The Superior rectal artery arises from the inferior mesenteric artery and then divides into two descending branches to run on either side of the rectum. In the majority (approximately 80%), the rectal blood supply comes from the superior rectal artery. Above the anus, each artery gives rise to several small branches which pass caudally and which are regularly spaced down to the level of internal anal sphincter, at which point they form loops around the caudal rectum and anastomose with other vessels.

The middle rectal artery arises from the internal iliac artery and approaches the rectum from the side immediately above the pelvic diaphragm and then joins superior rectal artery loop branches at the caudal end of the rectum and the upper anal canal.

The inferior rectal artery arises from the internal pudendal artery and passes medially through the ischiorectal fossa to the anal sphincter musculature and to the perianal skin.

The venous drainage accompanies the rectal arteries. In this respect, the superior rectal vein forms by approximately six ascending vessels which begin in the anal columns between the muscularis and the mucosa. The superior rectal vein drains directly into the inferior mesenteric vein. The middle rectal and inferior rectal veins drain into the internal iliac vein.

The lymphatic drainage of the rectum follows the arterial supply but in a cranial direction and to visceral lymph nodes. Intramural lymphatic vessels project to perirectal lymph nodes located within the fatty perirectal tissue which is completely enveloped by the mesorectal fascia. Lymphatic collection and drainage occurs unidirectionally towards the major lymph node stations along the superior rectal and the inferior mesenteric blood vessels [12]. Because of this arrangement, whilst performing a TME, the inferior mesenteric artery is commonly ligated high (at its origin from the aorta) in order to include apical lymph nodes within the resected specimen.

The principles of TME are based upon the embryology and anatomy of the rectum where the lymphatic drainage (which is associated with the arterial blood supply) is almost exclusively proximal and is generally confined within the mesorectal fascia. While the palpable luminal distal edge almost always corresponds to the histological distal extent of a rectal cancer, distal spread in the mesorectum is common and it is this feature that underlies the rationale for TME and which was one of Heald's earliest observations, particularly in bulkier tumours [1]. Distal mesorectal spread rarely extends, however, more than 2 or 3 cm beyond the lower palpable luminal edge of the tumour, though for safety reasons a distal mesorectal clearance of 5 cm, where feasible, is recommended [13, 14]. For mid- and low rectal cancers, the "total" mesorectum should be removed intact with the rectal muscle tube so in effect a minimum of 5 cm of distal mesorectum (a classical TME) should be performed for all rectal cancers dependent upon the height of the tumour.

For tumours of the upper rectum, the rectum and mesorectum can be divided 5 cm distal to the lower edge of the tumour and a mesorectal transection rather than a "total" mesorectal excision is deemed adequate. Mesorectal transection [15] rather than TME may reduce the incidence of post-operative surgical complications, particularly anastomotic leakage and is associated with better post-operative functional outcomes (mostly for reported evacuatory difficulty and stool frequency).

One of the major technical advances that facilitates safe restoration of intestinal continuity following a TME has been the development of anastomotic stapling instruments [5]. This, coupled with the recognition that adenocarcinoma rarely spreads distally in the muscle tube and that a 2 cm clearance beyond the macroscopic cancer in low tumours provides a safe distal margin, has permitted the policy that a distal margin of <1 cm may be oncologically adequate for ultra-low tumours [13].

Pre-operative Preparation

Mechanical bowel preparation is recommended if restorative anterior resection is planned and this strategy, although controversial is supported by a randomized controlled trial [16]. Sites for a possible defunctioning stoma should be marked by an enterostomal therapist on the awake patient sitting, lying and standing. Informed consent from the patient should include the risks of haemorrhage, anastomotic leakage and urinary and sexual dysfunction resulting from injury to the pelvic autonomic nerves during rectal mobilisation. In females the possible need for oophorectomy should also be discussed. It is the authors' policy to also consent patients for appendicectomy to treat synchronous, or avoid metachronous, appendiceal pathology including appendiceal neoplasia [17]. Prophylaxis against deep venous thrombosis is commenced using a combination of heparin or its analogues (depending upon the usage of epidural anaesthesia) and mechanical calf compression devices, once the patient is positioned on the operating table. Prophylaxis is continued through the post-operative period, including after hospital discharge [18, 19].

Patient Positioning

The lithotomy-Trendelenberg position, ensuring the patient is well down the table, is optimal as it allows per anal palpation and inspection, washout of the lumen and insertion of the circular stapling instrument to complete the anastomosis. The table is kept horizontal during the abdominal phase of the operation and the head is tilted down by 15–20°, or more, in order to facilitate pelvic dissection. It is important not to maintain too steep a Trendelenberg (head down) positioning for extended periods

so as to reduce the risks of lower limb compartment syndrome. If a steep position is used, the tilt should be temporarily reverted every 20–30 min for a period of 3–5 min.

A rectal examination should always be performed prior to painting and draping with the mandatory addition of a vaginal examination in females.

Operative Procedure

Open Case

A long vertical midline incision extending from the symphysis pubis to the epigastrium, and if necessary for safe splenic flexure mobilization to the xiphisternum, provides optimal access to the abdomen and pelvis.

The surgical procedure and sequence are planned. In this context, splenic flexure mobilization is almost always required for a colo-anal anastomosis so as to reduce anastomotic tension and in order to optimize the blood supply. This manoeuver is best performed at the beginning of the operation.

Splenic Flexure Mobilization

The operating surgeon stands on the left side of the patient with the first assistant on the patient's right. The assistant lifts the sigmoid colon anteriorly and to the right. The peritoneal reflection on the lateral side of the left colon (identified by the white line of Toldt) is divided by scissors or diathermy and followed cranially towards the splenic flexure. The plane of dissection in the left upper quadrant is developed between the colon and the urogenital structures. This most notably defines Gerota's fascia surrounding the kidney and the gonadal vessels, separating this from the colon rather than mobilization of specific lienocolic ligaments. The approach towards splenic flexure mobilization in robotic resection has presented specific difficulties and a medial to lateral dissection technique separating the flexure off the pancreas has been proposed [20]. Alternatives in this demanding aspect include a supramesocolic approach starting with the gastrocolic ligament, a lateral approach with coloparietal detachment which more typically resembles the open splenic flexure take-down and an 'inch by inch' approach dissecting the transverse mesocolon [21]. At this juncture, if the spleen is mobile on the diaphragm a large moist swab placed gently between the spleen and the diaphragm helps to push the spleen into view and facilitates splenic flexure mobilization.

The greater omentum is now retracted anteriorly and to the patient's left and the "bloodless" plane between the transverse colon and omentum is developed by sharp scissor dissection or by diathermy. The apex of the splenic flexure attachments (lieno-colic ligament) is visualized by downwards colonic traction from the patient's right with counter traction by a retractor under the left rib cage. The assistant

standing on the patient's right side maintains colonic traction and also insinuates the index finger of the right hand behind the colon on the left. This facilitates division of the apical lateral attachments by the operator who stands either on the patient's left side or temporarily between the patient's legs.

Ligation and Division of the Inferior Mesenteric Vessels

The left-sided colonic mobilization is continued inferiorly by the left-sided operator with identification of the ureter (usually positioned medial to the gonadal vessels and crossing the bifurcation of the common iliac artery at the apex of the sigmoid mesocolon) and the fascial covering of the uppermost part of the "mesorectal package". This manoeuvre is facilitated by the right-sided assistant applying traction on the sigmoid, anteriorly and to the right, taking care not to damage the mesentery of the colon. Once the plane has been developed at the pelvic brim to just beyond the midline, it is the authors' practice to insert a small swab behind the mesentery at the level of the pelvic brim. The sigmoid traction is now reversed and the assistant surgeon on the patient's right can identify the correct point to incise the right sided peritoneum by a combination of air in the tissues and anterior displacement of the mesentery by the small swab. The swab helps to protect the autonomic nerves at the level of the pelvic brim. The right-sided peritoneum is incised caudally to the pelvic brim and cranially towards the root of the inferior mesenteric artery. At this point the surgeon on the patient's left places the left index finger behind the pedicle and with left thumb anteriorly can palpate the inferior mesenteric artery between index finger and thumb. The peritoneal attachments are divided and the superior hypogastric plexus structures are mobilized away from the right side of the pedicle by sharp dissection. The index finger is then advanced cranially on the left side, parallel to the midline where a "window" in the mesocolon will be identified above the origin of the inferior mesenteric artery (IMA) between the aorta and the inferior mesenteric vein and the ascending left colic artery running side by side at this point. This window is opened and the autonomic nerves are again freed until the root of the IMA is clearly identified. It is important to check that the left ureter has not been elevated in this manoeuvre by visualizing the structures to the left of the pedicle. Once the IMA pedicle has been isolated it is clamped, divided and ligated approximately 2 cm from the aorta so as to reduce the risk of injury to the pre-aortic nerves and in order to achieve a "high" but not a "flush" tie of the IMA.

The inferior mesenteric vein (IMV) should next be divided, above its last branch, at the inferior border of the pancreas where is disappears cranially to join the splenic vein. This ensures maximum length and mobility of the left colon for later anastomosis. In 5–10% of patients a substantial branch of the superior mesenteric artery lies near the IMV at this point and judgement is required to determine if this vessel should be divided to facilitate colonic mobilization, or if it should be preserved where its division is likely to compromise colonic viability.

Mobilization of the Mesorectum and Rectum

This is oncologically one of the most important stages of the operation. The surgeon must develop a mental picture of the position and extent of the tumour, based upon the prior clinical and radiological assessment. The circumferential concepts of TME surgery are applied to ensure clear margins on the resected specimen. It is helpful to divide the descending colon at this stage, a so-called "division of convenience" using a linear cutting stapler. This facilitates the posterior pelvic dissection (Fig. 7.5).

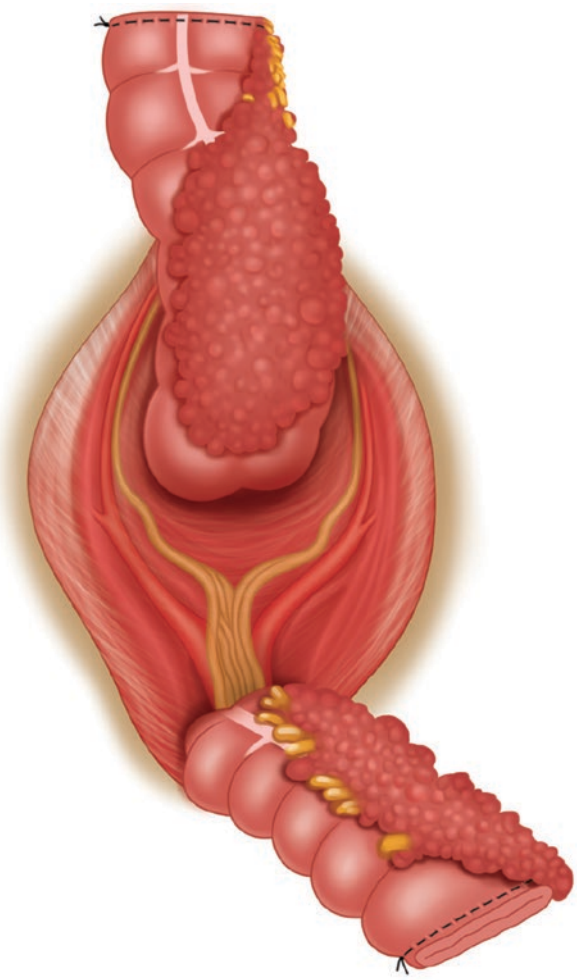

Fig. 7.5 Mobilization of the rectum and mesorectum. The colon has been divided using a linear cutting stapler and the posterior plane is being developed anterior to the superior hypogastric plexus and hypogastric (presacral) nerves

Posterior Dissection

The avascular areolar tissue plane (mesorectal fascia) which surrounds the mesorectum is identified and it is worth remembering that the mesorectum resembles a bilobed lipoma. The rectum is lifted gently forwards from the bifurcation of the hypogastric nerves and dissection commences in the midline using diathermy, aiming to minimize direct or collateral heat damage to the nerves. Dissection is extended downwards anterior to the curve of the sacrum on the surface of the mesorectal fascia. When there is sufficient space, a St Mark's rectal retractor is introduced behind the specimen. This helps to spread and "tent" the hypogastric nerves and aids identification. It is important to gently position the retractor and apply firm but gentle pressure to expose the mesorectal fascia and the layer of areolar tissue or what has been called the "angel hairs" in the plane where dissection should proceed. In this manoeuvre the operator (standing on the patient's left) and the first assistant (on the right) have to position and control the angulation and force of retraction, aided by the second assistant between the legs when more forceful retraction is needed. The angulation and degree of retraction are vital and are a dynamic activity that can only be controlled by direct vision such that an assistant between the legs can help but not position or alter the angle of traction.

It is important to note that all ***four hands*** of the operator and assistant are needed for retraction, counter-traction and dissection. A suction apparatus can be a useful retractor, in addition to its role in removing diathermy smoke and fluid. It is useful to wash out the pelvis on a regular basis, where the authors' preference is to use sterile water with dilute proflavine which is hypotonic and therefore cytocidal, as this helps to visualize the tissue planes.

Dissection then proceeds in the "angel hair" areolar tissue and should be predominantly from ***medial to lateral*** and from **below upwards** in an anterolateral direction allowing the hypogastric nerves to drop away posterolaterally. It is important to focus on "circumferential" mobilization rather than try to proceed too far posteriorly at this stage and dissection should progress laterally and then anteriorly on both sides.

Lateral Dissection

The lateral attachments are mobilized by extending the dissection plane forwards from the midline posteriorly around the sidewalls of the pelvis. It is important to remember that the inferior hypogastric plexuses (formed by the hypogastric nerves and the pelvic parasympathetic nerves) curve forwards tangentially around the surface of the mesorectum in close proximity. The nervi erigentes (pelvic parasympathetic nerves) lie more posteriorly in the same plane as the hypogastric nerves and should be visualized and preserved as they may be easily 'tented up' and damaged at this point. The nervi erigentes then curve forwards and converge like the base of

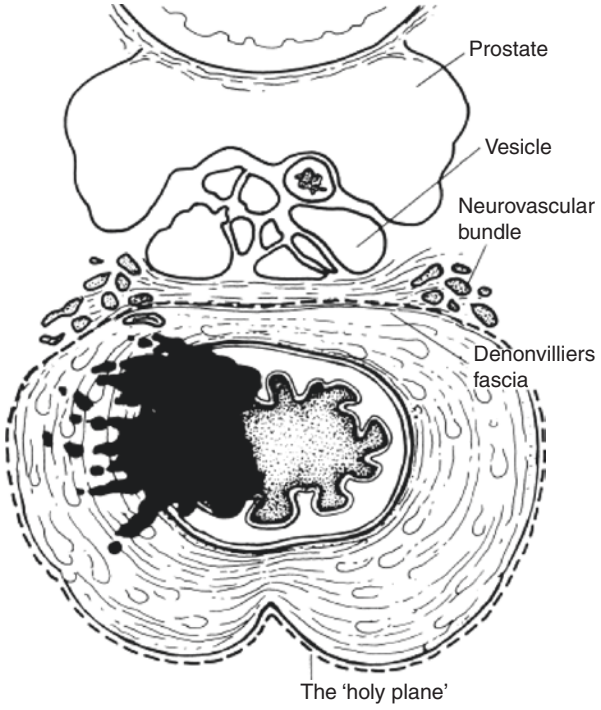

Fig. 7.6 Schematic outline of mesorectal fascia with the neurovascular bundles anterolaterally in the male pelvis. (Reproduced from [12] with permission from John Wiley & Sons)

a fan to join the hypogastric nerves and form the neurovascular bundles of Walsh [7–9] (Fig. 7.6).

Thus the nerves lie at the outer edges of Denonvilliers' fascia and are in danger of injury at the 10 o'clock and 2 o'clock anterolateral positions just behind the lateral edges of the seminal vesicles in the male. More distally they curve forwards and are less vulnerable to injury.

As the lateral dissection moves deeper into the pelvis, one or two middle rectal vessels may be encountered and occasionally may require to be occluded by precise diathermy or ligation. There are almost always some slender nerve branches here and these branches form the so called "lateral ligament". When medial traction is applied these branches will "tent" the plexus and it is important to divide them by sharp diathermy or scissor dissection close on the mesorectal surface. Previously described clamping of the "lateral ligaments" is unnecessary [22, 23]. If bleeding is encountered, it is often wise to place a pack gently on the area and move the dissection to another area, perhaps the other side or anteriorly.

Anterior Dissection

In males, the traditional teaching has been to incise the peritoneal reflection anteriorly, however, a better approach is to follow the plane forwards, from behind, anterolaterally on both sides until the seminal vesicles are visualized.

The plane immediately in front of Denonvilliers' fascia is developed by sharp dissection in the midline anteriorly. Dissection is then carefully extended laterally to meet the lateral dissection, remembering that the autonomic nerves converge to form the neurovascular bundles at the lateral edge of Denonvilliers' fascia. Denonvilliers' fascia also marks the anterior extent of the "tumour package" and lies like an apron anterior to the anterior mesorectum, behind the vesicles, until it fuses inferiorly with the posterior fascia of the prostate. For this reason, Denonvilliers' fascia must eventually be divided by scissors or diathermy to access the lowest few centimetres of anterior rectum. This should be well beyond the distal edge of the cancer except in the case of an ultra-low resection for a distal rectal cancer.

Anterior Dissection in the Female

In the female, the uterus, if present, should be lifted forward. There is a similar condensation of fibrous fascia here anteriorly, analogous to Denonvilliers' fascia in the male. It is often difficult to access the plane anterior to the recto-vaginal septum behind the cervix and posterior fornix and this plane is best approached, as in the male, by continuation of the anterolateral dissection from the side wall. Troublesome bleeding may be encountered from the vaginal venous plexus. Attempts to control the bleeding may be futile until the vagina has been fully mobilized off the anterior rectum allowing the stretched venous plexus to collapse down. The peritoneal reflection may be adherent to the posterior fornix and require dissection away with the diathermy.

Involvement of the Uterus or Vagina

Involvement by tumour of the uterus or the vagina is usually detected during pre-operative imaging and/or during vaginal examination prior to surgery. A large fixed cancer, even with neoadjuvant chemo-radiotherapy, is best removed by *en bloc* resection of the uterus and rectum with as much of the posterior vaginal wall as is needed. The vagina may be closed primarily in most patients but if the defect is large, particularly in a sexually active patient, reconstruction using a musculocutaneous flap may be needed [24].

Anterior Dissection in the Male

Involvement of Seminal Vesicles or Prostate

The vesicles on one or both sides may be removed *en bloc* with the rectum taking care to identify and preserve the ureters. Ureteric stenting in such cases is prudent. Prostatic involvement is more problematic, however, and may require pelvic

exenteration or in selected cases a nerve preserving prostatectomy *en bloc* with the rectum. Modern MRI imaging should predict this eventuality. The opinion and involvement of an experienced urologist is needed in such cases, with some reporting a lower complication rate and a lower urinary leak rate for the *en bloc* approach [25, 26].

Distal Washout and Anastomosis

When the rectum is fully mobilized to the anorectal muscle tube an occlusion clamp or linear stapler is placed across the muscle tube, at least a finger and thumb's breadth below the lower edge of the tumour. A novel "Triple" stapling technique has been described to facilitate this in a low rectal cancer using a 45 mm or 30 mm linear stapler [5, 14, 27].

A proctoscope is then introduced into the lumen of the anal canal, below the occlusion clamp or staple gun, which is then irrigated using a 50 ml bladder syringe or a catheter irrigation system with water, povidone iodine or a dilute proflavine solution. Once the washout is complete, a second linear stapler is applied distal to the occlusive staple line and fired across the washed muscle tube. For very low tumours, two 30 mm linear staplers are optimal (Fig. 7.7). The muscle tube is sectioned with a scalpel on the *upper edge of the distal stapler* as shown after rotating the proximal stapler horizontally to provide a transection area.

The rectum is then removed and the distal margin on the resection specimen is inspected and palpated in order to ensure that it is clear of the tumour prior to removal of the distal stapler. If there is doubt, the staples may be removed and the lumen inspected directly. Where clearance is marginal, another linear stapler can be positioned below the *in-situ* anorectal tube stapler so as to obtain further clearance. Once the surgeon is satisfied with the margin the distal linear stapler is removed.

The pelvic cavity is then lavaged and inspected for bleeding. Haemostasis is secured with carefully applied diathermy or suturing on occasion where necessary. For troublesome presacral, pelvic side-wall or other bleeding a haemostatic agent, such as Tachosil™, may be helpful. Rather than repeated futile attempts at diathermy or suturing, packing of the pelvis will usually arrest bleeding if left in place for at least 10–15 min.

Following a TME, a 'neorectal' reservoir is recommended as the functional outcome is better in the early postoperative period when compared with a straight colonic anastomosis [4, 28]. This issue is covered in more detail in another section of this chapter. A side (colon)-to-end (anorectum) anastomosis or a short 5 cm colonic 'J' pouch appear equally effective. The authors' preference is for "a side-to-end" Baker style technique [28], placing the spike of the detachable anvil through

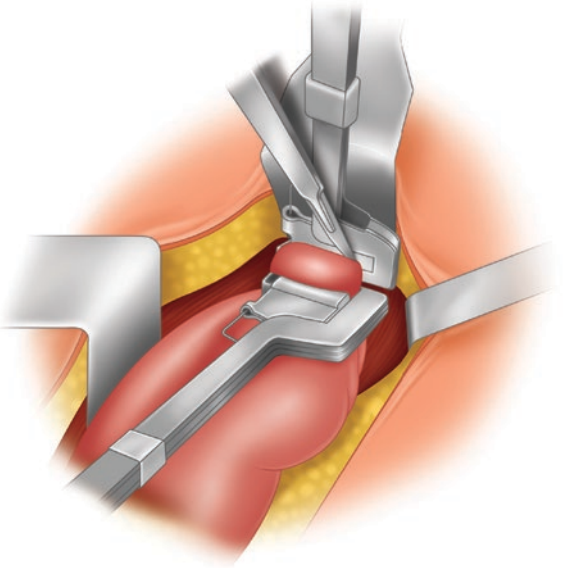

Fig. 7.7 The muscle tube is sectioned between two 30 mm linear staplers in the "Moran Triple Stapling Technique" for low rectal cancer. (Manual of Total Mesorectal Excision, Moran and Heald, Copyright (2018), reproduced by permission of Taylor & Francis Books UK)

the opened end of colon, spike first, through the anterior mesenteric border approximately halfway between the taenia coli and approximately 4 cm from the colonic end. The colonic opening is then closed using either staples or sutures.

Circular Stapled Anastomosis

The anorectal remnant is palpated from between the legs. The anal canal may have to be dilated gently so as to accommodate the lubricated circular stapler. Relaxation of the sphincter by anal application of glyceryl trinitrate (GTN) (cream applied 30–60 min, or alternatively with sublingual GTN spray 5 min beforehand) may facilitate introduction of the stapler. Care must be taken not to disrupt the transverse staple line and the abdominal surgeon may have to bimanually assist in this step to ensure safe placement. A St Mark's retractor helps to visualize the anorectal stump and retract the seminal vesicles and the prostate in the male, (or the vagina in the female), anteriorly. Once the circular ring of the gun is visible clearly through the bowel wall the gun is opened and the protruding spike guided through the bowel, ideally just behind the linear staple line. The head of the gun is brought down and engaged with the shaft. The gun is slowly closed until the tissues are in apposition as seen on the tissue indicator mechanism on the circular gun.

At this point it is mandatory to check the alignment of the proximal colon (including the transverse colon) to ensure that there is not a 360° twist of the colonic mesentery prior to firing the stapling instrument. The circular stapler is fired according to the specific manufacturer's instructions. The anastomosis is gently palpated for integrity and can be air-tested by filling the pelvis with water and insufflating air via the anal canal, using a syringe or a proctoscope. If an air leak is identified, this should be repaired with interrupted sutures, if necessary using a trans-anal approach.

Defunctioning a Low Anastomosis After TME

Even if the anastomosis is airtight, consideration should be given to a temporary defunctioning stoma and there are some surgeons who will use this in all cases of a colo-anal anastomosis after a TME. A recent randomized trial by Matthiessen et al. [29] reported a 28% leak rate in patients after TME without a defunctioning stoma compared with a 10% incidence of leak in those with a loop stoma. Factors which have been shown to increase the risks of anastomotic leakage include the height of the anastomosis from the anal verge (particularly when it is performed below 5 cm which includes all patients after a TME), the use of preoperative chemoradiotherapy, intra-operative technical difficulties (such as major bleeding) and male gender. A defunctioning stoma will reduce the consequences of any anastomotic leak and the need for an emergency re-operation [30, 31]. A defunctioning loop ileostomy or transverse loop colostomy may be closed 6–8 weeks later following a contrast enema to ensure there is no leak. Debate exists concerning the optimal proximal diversion with most preferring a loop ileostomy over a transverse colostomy although the comparative data are conflicted. Both methods provide an acceptable diversion with low complication rates where Klink et al. [31] have shown a higher wound infection rate with colostomy reversal and a higher incidence of significant dehydration and renal insufficiency with an ileostomy, the use of which may be precluded in some elderly patients where it might be anticipated that fluid derangement will not be tolerated.

If a temporary stoma has not been placed and there are concerns in the postoperative period regarding an anastomotic leak, a CT scan with rectal contrast should be expedited. If detected, an emergency re-operation is often required and may entail anastomotic excision with an end colostomy. In selected patients, however, the anastomosis can be preserved with the use of broad spectrum antibiotics, adequate drainage of any collections and defunctioning with a proximal loop stoma. Recently, minor anastomotic leaks after a low anterior resection with a pre-existent proximal stoma may be managed by endoanal drainage preserving the anastomosis and utilizing a range of endoanal therapies including the use of a vacuum-assisted endosponge, anastomotic stenting and endoclip application [32, 33].

Whilst there is ongoing debate concerning the need for drainage after colorectal surgery, it currently remains the authors' preference to insert two low-pressure, closed suction drains placed in the presacral cavity which are typically removed at about 48 h postoperatively.

Laparoscopic and Robotic TME

This chapter mainly focuses on the technique of open TME, however the 'circumferential awareness' and principles of dissection in the correct planes safeguarding autonomic nerves remain the same in laparoscopic or robotic TME. These techniques are covered elsewhere in other sections of this book. One of the main technical differences in laparoscopic/robotic surgery as against open anterior resection is the preference to take down the inferior mesenteric artery and vein prior to the lateral mobilisation of the left colon with dissection occurring usually from medial to lateral. In essence, where expertise is available all indications and contraindications for open techniques and for ancillary neoadjuvant therapy should be able to be translated to the laparoscopic/robotic approaches [34].

Oncological Outcomes of TME

Historically rectal cancer was associated with a high local recurrence rate attributable to the anatomy of the rectum and technical difficulties operating in the confines of the narrow pelvis [7]. In trial reports from the 1980's and 1990's from Denmark [35], the Netherlands [36] and the United Kingdom [37] reported local recurrence rates of 18%, 33% and 34% respectively. The addition of postoperative radiotherapy had no significant effect in reducing local recurrence [38]. There have been a number of studies assessing the role of pre-operative short-course radiotherapy (25 Gy in daily 5 day fractions) in reducing local recurrence. The Swedish trial in 1997 reported a reduction in local recurrence from 27% to 11%, and an increased overall survival from 48% to 58% [39]. However the surgery in this trial was not standardized and other studies were unable to reproduce a survival benefit [40].

Prior to this Heald and colleagues [41] had reported a local recurrence rate of 2.7% and an overall cancer-specific survival of 87.5% at 5 years in curative anterior resection treated by TME surgery alone. The Dutch Colorectal Cancer Group combined the concepts of TME with short-course preoperative radiotherapy in an elegant randomized controlled trial of TME alone compared with pre-operative radiotherapy prior to TME [42]. In this study, the local recurrence rate was 8.2% with TME alone compared with 2.4% in patients who underwent preoperative radiotherapy and TME. Similarly in the MRC CR07 trial published in 2009

[43], the local recurrence rate was 4% in patients who received preoperative radiotherapy and TME compared with 10% in those randomized to TME (combined with postoperative chemoradiotherapy in those with an involved CRM). A key finding in CR07 was that the quality of the specimen correlated with the local recurrence rates and the best outcomes were reported after mesorectal plane dissection when compared with intra-mesorectal or mucularis propria dissection planes [44].

One of the key benefits of TME has been a reduction in the incidence of circumferential resection margin (CRM) involvement due to the standardized focus on peri-mesorectal fascial dissection to optimize the quality of the specimen. This is crucial as preoperative, or postoperative radiotherapy does not significantly reduce the local recurrence rate when the CRM is involved (as defined by tumour at or <1 mm from the resection margin) [45]. In the Dutch trial, the 5-year local recurrence rates and overall survival rates were 23.7% and 44.5%, respectively when the CRM was 0–2 mm. compared with 8.9% and 66.7%, respectively with a CRM > 2 mm respectively suggesting that adequate margin clearance is crucial for both a reduction in local recurrence and for optimizing survival [46].

There has been ongoing debate concerning the effect of involved mesorectal lymph nodes on local recurrence, with some conflicting reports. It has been suggested that, if a TME is performed, local recurrence rates of <10% can be achieved, even in node-positive rectal cancer [47] and that lymph node status does not predict local recurrence in the modern TME era [48]. A further contentious issue is the differential outcome in rectal cancer treated by abdomino-perineal excision (APE) compared with patients who have a restorative anterior resection where there appears to be a worse disease-free survival, overall survival and cancer-specific survival in patients who had undergone an APE [49]. Whilst it is hypothesized that this may be a feature of the technique of APE itself, it is more likely that this effect is predominantly related to the inherently adverse features of rectal cancers that require an APE in the first place [50].

Recent reports have outlined the complexity of low rectal cancer (as defined by a cancer with its lower margin, at or below, the origin of the levator on the pelvic sidewall) [51]. In this regard, Moran et al. have outlined the need to focus on clinical assessment, with optimal radiological imaging using pelvic MRI, the need for selective preoperative therapy and attention to the details of the surgery with the additive concept of an extra-levator approach to an APE for advanced low rectal cancers [52]. For all of these patient groups both function and the quality of life need careful consideration particularly in ultra-low cases where a low anastomosis is contemplated and for those in this circumstance undergoing neoadjuvant treatment.

Neo-rectal function following AR has been shown to be influenced by age, gender, the height of anastomosis from the anal verge, exposure to neoadjuvant radiotherapy and the preoperative sphincter function. Female patients and a low anastomosis have been found to be the two most significant factors in one such study [53]. The features affecting neo-rectal function and the risks of leakage in a low anastomosis are critical factors for consideration, particularly in low rectal cancer where TME and a colo-anal anastomosis is deemed oncologically feasible [54].

In this group of patients, anastomotic leakage has an associated mortality in the range of between 6% and 22% and its clinical course will delay reversal of a defunctioning stoma so much so that in some series over half of the patients who experience a significant leak will effectively have a permanent stoma which is never reversed [55]. The benefits of defunctioning a low anastomosis have been demonstrated in this clinical context in an elegant Swedish randomized controlled trial by Matthiessen et al. [56].

Conclusion

The concept of TME is based upon the embryology and the anatomy of the rectum and the surgical principles aim to remove the cancer with its surrounding mesorectum contained within the mesorectal fascia. Optimal staging by high quality MRI, selective use of neoadjuvant therapy and the adoption of the surgical concepts and standardized principles of total mesorectal excision (TME) result in curative treatment for the majority of patients with rectal cancer. Perhaps the Swedish experience is most stark where the introduction of a TME programme alone (even in the absence of these other recommended techniques and investigations tailoring rectal cancer management to the patient) resulted in a reduction of the locoregional recurrence rates from 21.9% to 8.2% over a 1-year introduction of the TME technique in Stockholm in 1994 [55]. This benefit was accompanied by a reduction in the permanent stoma rate from 60.3% to 26.5% and an improvement in the 5-year cancer-specific survival from 66% to 77.3% overall.

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Chapter 8
The Impact of Minimally Invasive Technology in Rectal Cancer

Jason R. Bingham and Scott R. Steele

Introduction

Rectal cancer remains a common and complex surgical problem worldwide. Despite significant advancements in treatment over recent decades, colorectal carcinoma persists as the second leading cause of cancer-related deaths in Western countries. Each year approximately 40,000 new cases of rectal cancer will be diagnosed in the United States, comprising nearly 30% of all colorectal malignancies [1]. Since its inception, minimally invasive surgery (MIS) has made substantial progress in the treatment of both benign and malignant colorectal disease. MIS offers the well-known benefits of a shortened hospital stay, earlier return of bowel function, less postoperative pain and decreased intraoperative blood loss when compared with open surgery [2–4]. However, these benefits must be weighted in accordance with the oncologic results.

Certainly, the surgical success with any cancer resection is dependent upon the oncologic outcome. Initially, the application of minimally invasive techniques to malignant colorectal disease was questioned due to concerns regarding its oncologic equivalence to open surgery. However, several large-scale trials comparing laparoscopic versus open surgery for colon carcinoma demonstrated equivalent

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J. R. Bingham
Department of General Surgery, Madigan Army Medical Center, Tacoma, WA, USA

S. R. Steele (✉)
Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA
e-mail: steeles3@ccf.org

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oncologic outcomes and clear short-term advantages with laparoscopic approaches [3, 5–10]. The most notable of these were the Clinical Outcomes of Surgical Therapies (COST), the Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC), and the Colon Cancer Laparoscopic or Open Resection (COLOR) trials. MIS for the treatment of colon cancer is now well established and laparoscopic resection is a widely accepted alternative to open surgery for colon cancer.

The treatment of rectal cancer, however, is a separate entity from that of colon cancer and poses unique challenges to the surgeon. The pelvic dissection required can be quite difficult given the confines of the bony pelvis and limited visual exposure, especially in obese patients and when operating within the male pelvis. Distorted planes due to neoadjuvant radiation therapy or large tumors invading surrounding structures further increase the technical complexity. In addition, the technique of total mesorectal excision (TME) has clearly been shown to result in improved oncologic outcome and has become the gold standard in the surgical treatment of rectal cancer [11–13]. This is a technically challenging procedure which adds to the complexity of an already difficult surgical disease. These facts have left many questioning if an acceptable oncologic resection can be reliably achieved using minimally invasive techniques. Interestingly, with the exception of the CLASICC trial, none of the above mentioned studies included cases of rectal cancer in their analysis. Moreover, the CLASICC trial actually fueled concerns as it demonstrated a non-significant trend towards higher rates of positive circumferential resection margins in those undergoing laparoscopic anterior resection when compared with those who underwent open resection (12% vs 6%, P = 0.19) [7].

It remains important to note that this trend resulted, however, in neither an increased recurrence rate nor a decreased survival rate in long-term follow up [14]. This study by Green et al. assessed the long-term outcomes in the UK MRC trial (median follow-up 69.2 months, range 22.9–92.8 months) showing no differences in overall or disease-free survival with a trend in colonic cases which underwent open conversion for a negative overall cancer-specific survival impact. Nevertheless, the application of MIS for the treatment of rectal cancer has remained a matter of debate largely because of study heterogeneity. The Comparison of Open versus laparoscopic surgery for mid and low Rectal cancer After Neoadjuvant chemoradiotherapy (COREAN) randomized trial found no difference in recurrence or survival between techniques in 3 year follow up [15]. The COLOR II randomized trial, that included 1044 patients in 8 countries also found no differences in locoregional recurrence, disease free survival, or overall survival at 3 years [16].

However, superiority of short term outcomes was not supported in the American College of Surgeons Oncology Group (ACOSOG) Z6051 study [17], which enrolled a large proportion of patients with distal cancers, and the Australian and New Zealand Laparoscopic-Assisted Resection versus Open Resection (ALaCaRT) [18]. These are both randomized trials comparing laparoscopic to open techniques in rectal cancer only. Long-term outcomes are awaited from these trials.

It may ultimately be found that an equivalent oncologic outcome can be achieved using minimally invasive techniques when compared with open surgery for rectal cancer. This chapter will review current minimally invasive options and their respective outcomes specifically in the treatment of rectal cancer.

Laparoscopic Total Mesorectal Excision

Advantages

Laparoscopic resection of rectal cancer offers many potential advantages when compared with open resection. The short-term advantages of MIS have been well described. These include a faster return of bowel function, a reduced length of hospital stay, less wound complications, reduced pain with lower narcotic use, decreased intraoperative blood loss, and earlier postoperative ambulation. Laparoscopy has the additional advantages of lower hernia rates and decreased adhesion formation, which may have long-term benefits. In addition, there are several theoretical benefits of MIS specific to the treatment of rectal cancer. The preservation of urinary and sexual function may be improved as the magnification of the surgical field offered by laparoscopy allows a more precise sharp dissection and better preservation of hypogastric and pelvic splanchnic nerves. However, the data are conflicting on this theoretical benefit and further investigation is needed before any definitive conclusions can be made [19, 20]. Another potential benefit of MIS with rectal cancer resection is that a shorter recovery time may lead to earlier treatment with adjuvant chemotherapy. This, in turn, could have significant implications with regard to oncologic outcome. While there is some evidence that patients who undergo laparoscopic resection receive adjuvant therapy earlier than patients undergoing open surgery, the survival benefit of this has yet to be proven [21]. Nevertheless, this remains a promising notion.

Techniques and Outcomes

Laparoscopic low-anterior resection (LAR) for rectal cancer involves mobilization of the left colon and splenic flexure, ligation of the inferior mesenteric vessels at their origin and rectal mobilization and dissection of the rectum in an avascular plane (Fig. 8.1). This is followed by transection of the rectum at the pelvic floor (Fig. 8.2) with either intra- or extra-corporeal resection and a stapled coloanal anastomosis (Fig. 8.3). Since first introduced by Heald in the 1980s, Total Mesorectal Excision (TME) has become the gold standard in the surgical treatment of rectal cancer and has been clearly shown to reduce local recurrence rates and improve oncologic outcomes [11–13]. The technique involves meticulous sharp dissection

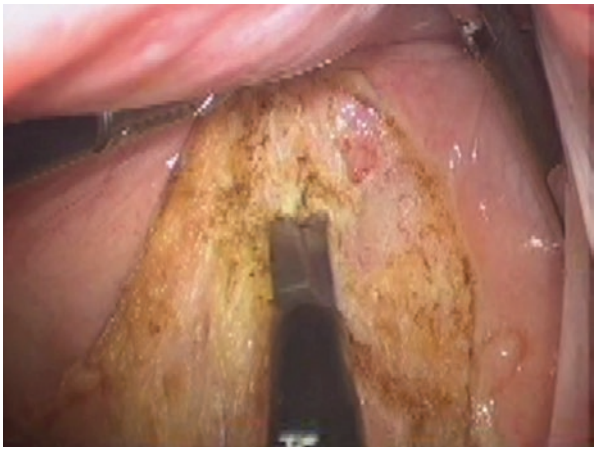

Fig. 8.1 Laparoscopic dissection in the anterior plane in a female patient. Care must be taken in dissection of the rectogenital fascia to avoid entering the vagina

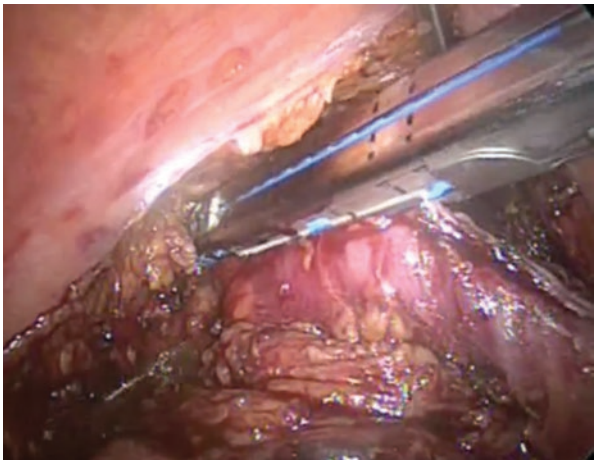

Fig. 8.2 Laparoscopic distal transection of the rectum. Perineal pressure may provide an additional ability to place the stapler closer to the anorectal ring

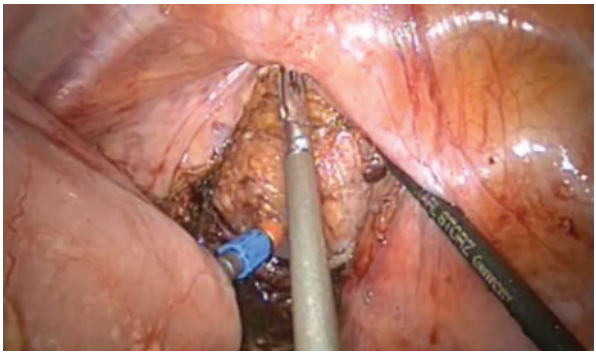

Fig. 8.3 Straight laparoscopic stapled coloanal anastomosis. Care needs to be taken to ensure the prostate/vagina is kept clear of the staple line

under direct vision in the avascular plane between the visceral and parietal layers of pelvic fascia, thus incorporating the entire mesorectum and its associated lymphatics as described in detail elsewhere in this book section.

While the non-oncologic benefits of laparoscopic resection are clear, its use can only be justified in light of its success with regard to oncologic outcome. Following the initial concerns raised by the CLASICC trial, in which laparoscopic resection showed a non-significant trend toward increased rates of positive circumferential margins compared with open resection, several randomized controlled trials have further investigated the oncologic success of laparoscopic resection of rectal cancer (Table 8.1) [7, 9, 15–18]. Numerous trials have since shown no difference with regard to adequacy of resection specimen or in the number of lymph nodes harvested [9, 22–26]. More importantly, the 5-year overall survival, disease-free survival, local recurrence and distal recurrence rates have all been demonstrated to be equivalent between laparoscopic and open resection (Table 8.1) [15, 16, 24]. The oncologic equivalence of laparoscopic to open surgery has been supported by several meta-analyses, which have found no difference between the groups in overall survival, disease-free survival, local recurrence rates, the number of lymph nodes harvested, or the rate of positive specimen resection margins [27–30]. However, two of the more recent randomized trials performed in the United States, and in Australia/New Zealand could not conclude that laparoscopic TME was non-inferior to open surgery based on evaluation of the TME specimen. Both trials used the same oncologic primary endpoint- a composite of positive CRM, or positive distal margin, or incomplete TME. Incorporating these trials, a recent systematic review found positive CRM rates of 7.9% in laparoscopic and 6.1% in open proctectomies ($p = 0.26$), but significantly more inadequate TMEs in laparoscopic versus open cases (13.2% versus 10.4%; $p = 0.02$) [31].

In addition to the oncologic success of the resection, equivalence or superiority of MIS with regard to perioperative mortality and morbidity is vitally important prior to widespread acceptance. Several large-scale clinical trials have demonstrated perioperative morbidity and mortality to be similar between laparoscopic versus open TME for rectal cancer [9, 23–26]. Postoperative anastomotic leak is a dreaded complication and is of particular concern following laparoscopic low anterior resection (LAR) given the technical difficulty of the coloanal anastomosis. However, the preliminary short-term results from the laparoscopic versus open surgery for rectal cancer (COLOR II) trial demonstrated no significant difference in postoperative leak rates between laparoscopic and open resections (13% vs 20%, $p = 0.462$) [32]. Additionally, a meta-analysis conducted by Arezzo et al. [33] including over 4500 patients actually demonstrated a lower overall complication rate (31.8% vs 35.4%, $P = <0.001$) with laparoscopic resection when compared with open surgery for rectal cancer. This supports the impression that mortality and morbidity are at least comparable between the two groups and potentially even lower with a laparoscopic approach. Moreover, many randomized controlled trials have confirmed that the well-known benefits of laparoscopy are seen when applied to cases of rectal cancer; to include less blood loss, shorter hospital stay, faster return of bowel function and reduced narcotic requirement. Therefore, there is sufficient evidence to say that

Table 8.1 Randomized controlled trials on laparoscopic vs open surgery for rectal cancer

	Patients included	Follow-up	Positive CRM	Operative time (min)	Blood loss (ml)	Overall complication	Local recurrence	Disease-free survival	Overall survival
Braga [9]	168	53.6 mo. (mean)	1.2% *vs* 2.3% (p = NS)	262 *vs* 209 (p = <0.001)	213 *vs* 396 (p = 0.0002)	24% *vs* 34% (P = 0.18)	4% *vs* 5.2% (P = 0.97)	60–90% (p = NS)	60–90% (p = NS)
Guillou and Green [7, 14]	381	62.9 mo. (median)	16% *vs* 14% (p = 0.8)	180 *vs* 135	NA	18% *vs* 14% (p = NS)	15.3% vs 9.9% (p = NS)	70.8% *vs* 67.1 (p = 0.925)	82.7% *vs* 65.8% (p = 0.147)
Liang [26]	343	44 mo. (median)	NA	138 *vs* 118 (p = <0.001)	NA	NA	NA	NA	76% *vs* 82.8% (p = NS)
Kang and Jeong [15, 25]	340	48 mo. (median)	2.9% *vs* 4.1% (p = 0.77)	244 *vs* 197 (p = 0.0001)	200 *vs* 217 (p = 0.006)	21.2% *vs* 23.5% (p = 0.603)	2.6% *vs* 4.9% (p = NS)	79.2% *vs* 72.5% (p = NS)	91.7% *vs* 90.4% (p = NS)
Lujan [23]	204	32.8 mo. (mean)	4% *vs* 2.9% (p = 0.422)	193 *vs* 172 (p = 0.02)	127 *vs* 234 (p = <0.001)	33.7% *vs* 33.0% (p = 0.956)	4.7% *vs* 5.3% (p = 0.781)	84.8% *vs* 81.0% (p = 0895)	72.1% *vs* 75.3% (p = 0.98)
Ng [24]	153	112.5 mo. (median)	2.6% *vs* 1.3% (p = 0.62)	213 *vs* 154 (p = <0.0001)	280 *vs* 337 (p = 0.338)	30.3% *vs* 31.2% (p = 0.903)	7.1% *vs* 4.9% (p = 0.677)	82.9% *vs* 80.4% (p = 0.698)	63.9% *vs* 55.1% (p = 0.303)
Bonjer [16]	1044	36 mo	10% vs 10%	NA	NA	NA	5.0% vs 5.0% (p = NS)	74.8% vs 70.8% (p = NS)	86.7% vs 83.6% (p = NS)
Fleshman [17]	262	NA	12.1% vs 7.7% (p = 0.11)	266 vs 221 (p < 0.001)	256 vs 318 (p = 0.004)	57 vs 58 (p = 0.93)	NA	NA	NA
Stevenson [18]	475	NA	7% vs 3% (p = 0.06)	210 vs 190 (p = 0.007)	100 vs 150 (p = 0.002)	20 vs 27 (p = NS)	NA	NA	NA

when performed by properly trained and experienced surgeons, laparoscopic resection and total mesorectal excision for rectal cancer appears to have equivalent short- and long-term oncologic outcomes, at least as good of morbidity and mortality rates, and short-term non-oncologic benefits when compared with open surgery.

Hand-Assisted Laparoscopy

A purely laparoscopic TME is technically very difficult with a steep learning curve. Obtaining proper operative exposure in the narrow confines of the pelvis can pose a daunting challenge. An alternative technique useful to facilitate exposure with rectal dissection is hand-assisted laparoscopic surgery (HALS) [34]. HALS is a hybrid procedure that utilizes laparoscopic techniques together with a hand-access port which allows the surgeon the ability to place his/her hand into the abdomen while still maintaining pneumoperitoneum. This provides tactile feedback to aid in retraction and exposure, thus facilitating accurate sharp dissection. It is thought that this can decrease the technical difficulty of the procedure and potentially shorten the learning curve. The use of HALS has been shown to both shorten operative times and decrease rates of conversion to open surgery [35, 36]. Additionally, there is evidence that more patients may potentially benefit from MIS due the use of HALS, as it has been shown that more complex and extensive resections are being attempted and completed laparoscopically when the technique is used [37]. Meta-analysis comparing HALS with conventional laparoscopic-assisted approaches has shown a lower conversion rate for the HALS cases with equivalent morbidity rates with an offset cost because of reduced operative time [38].

Limitations

Despite the many advantages of laparoscopic TME, many limitations exist. The view obtained by traditional laparoscopic cameras is assistant-dependent, two-dimensional and often sub-optimal. Frequently, the view is further obscured by fumes from energy sources activated in the confined space of the pelvis. Straight laparoscopic instruments with fixed tips have generally poor ergonomics and limit the dexterity of the surgeon, making high precision dissection and suturing difficult. HALS can help mitigate some of these limitations although it should be no surprise that there is a steep learning curve associated with both rectal procedures. HALS still uses a triangulated dissection technique so that the device should not be placed directly over the target organ and decisions of site use will rely on where it is deemed that open conversion can be conducted with ease when necessary. In addition, in cases with large tumors or a narrow pelvis, the hand may limit visualization, as there is simply not enough room for safe dissection. Although the learning curve with HALS may be reduced its use still requires the mastering of laparoscopic skills with

the HALS providing early tactile sensation reducing operative time and blood loss in advanced and bulky cases. These shortcomings are significant and it has been proposed that they can be addressed more successfully with robotics, though without rigorous data, this area remains controversial.

Robotic Total Mesorectal Excision

Advantages

The use of robotic surgical systems has several potential advantages that may help overcome some of the limitations of traditional laparoscopic surgery, while still preserving the benefits of a minimally invasive approach. First, it provides a stable, surgeon-operated camera that gives a clear three-dimensional view. Second, rather than tremor amplification, which is a characteristic of standard laparoscopy, the robotic system actually filters physiologic tremor. Third, surgical maneuvering is more comfortable and natural owing to instruments that allow multiple degrees of freedom and intuitive "wrist-like" manipulation. For these reasons, it has been suggested that the robotic platform may have a shorter learning curve when compared with traditional laparoscopy for rectal surgery [39].

Techniques and Outcomes

Several robotic techniques for resection of rectal cancer have been described and as experience with the platform grows the approaches will continue to evolve. The operative steps for rectal resection are conceptually the same as for traditional laparoscopy. However, unique challenges arise with a robotic approach when operating in separate abdominal quadrants as repeated docking and undocking of the robotic cart are often necessary. Some prefer a totally robotic approach by mobilizing the left colon and then repositioning the robot for the rectal dissection [40]. Others utilize a hybrid procedure, in which traditional laparoscopy is used for left colon mobilization and inferior mesenteric vessel ligation, followed by robotic pelvic dissection and TME (Fig. 8.4). A technique for performing a single-docking robotic low-anterior resection has been described [40]. Proponents of the hybrid technique argue that the totally robotic approach is time consuming and that the only true benefit for the robot is seen with the rectal dissection and TME component. Others argue that robotic dissection around the IMA pedicle is important to help preserve the periaortic nerves and consequently, urinary and sexual function [41].

The application of robotic systems to the resection of rectal malignancy is in its early stages, and there are currently limited data concerning the oncologic outcome of robotic TME. Nevertheless, several comparative studies demonstrate

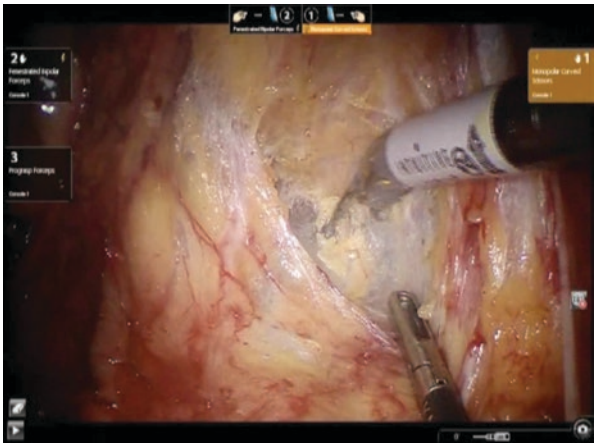

Fig. 8.4 View of a robotic dissection in the posterior avascular presacral plane during total mesorectal excision. (Courtesy of Alessio Pigazzi, MD)

equivalence in the quality of TME specimen and in the number of lymph nodes removed when compared with a traditional laparoscopic approach [42–44]. The short-term non-oncologic benefits of robotic TME also appear to be similar to those seen with standard laparoscopic resection. Recent systematic reviews comparing robotic with laparoscopic colorectal surgery found similar rates of postoperative complications and no significant difference with regard to length of hospital stay, blood loss, or return of bowel function between the two groups [42, 43]. Unfortunately, the perceived benefit regarding the preservation of pelvic autonomic nerves has yet to be proven, as no significant difference in rates of urinary and fecal incontinence or sexual dysfunction have been seen between robotic or laparoscopic resections [44].

Interestingly, there is some data to suggest lower conversion rates and lower anastomotic leak rates when a robotic approach is applied to a select patient population. A recent systematic review demonstrated a non-significant trend toward a lower conversion rate overall in those undergoing robotic resection (1–7.3%) compared with standard laparoscopic resection (3–22%), despite having a higher number of patients with prior abdominal surgeries, low rectal tumors and previous neoadjuvant chemoradiation therapy (CRT). Similarly, no significant difference has been reported in anastomotic leak rate between the two groups (7.6% vs 7.3%, p = NS), again despite a higher number of patients who had received neoadjuvant CRT in the robotic resection group [43]. The RObotic versus LAparoscopic Resection for Rectal cancer (ROLARR) trial, a large-scale, multi-center, (multinational) randomized controlled trial randomized 471 patients to robotic-assisted or laparoscopic proctectomy [45, 46]. The primary outcome was conversion to open procedures, and this was found to be no different between groups (8.1% in the laparoscopic group; 12.2% in the robotic-assisted group; p = 0.16). Secondary endpoints of postoperative complications, short-term urinary and sexual function, and anastomotic leak, were no different between groups. Oncologic outcomes of

CRM positivity and quality of mesorectal dissection was similar in both groups. Long-term outcomes are awaited. So far, the evidence suggests that robotic surgery shows no disadvantages with regard to short term complications and the quality of surgery.

Limitations

The surgical robot system has the potential to be an enabling technology that allows a greater number of patients to benefit from MIS. Nevertheless, current systems have significant limitations that must be improved upon with future platforms in order to justify more widespread use. Preoperative positioning must be very precise to provide the optimal working field and to prevent intraoperative arm collisions. Moreover, once the system is docked, the undocking and repositioning process, although often required when operating in multiple abdominal quadrants, can be time consuming and cumbersome. Additionally, there are currently a limited number of surgical instruments, staplers, and energy sources that are compatible with the system, although the selection is likely to significantly increase as the technology achieves more generalized use. Another clear limitation of current systems is the lack of both tactile sensation and tensile feedback. The operating surgeon is forced to rely upon visual cues in order to determine the amount of tension being applied to a particular tissue. Thus, tissues can be easily damaged if too much force is inadvertently applied with the robotic instruments.

Perhaps one of the biggest impediments to the more widespread application of robotic systems is the significantly higher cost over both open and laparoscopic approaches. This issue is addressed elsewhere in this book. While standard laparoscopy is associated with a higher operative cost than open surgery, the cost can (1) be justified by clear and significant patient benefits and (2) be offset by a shorter hospital stay. The authors of ROLARR calculated that all robotic procedures would need to exceed an average net benefit of $1611 per case, which was not found in the trial. In fact, robotic assisted cases were $1132 more expensive, mostly driven by higher intraoperative costs. With both higher start-up and running costs and no clear benefit over traditional laparoscopy, the implementation of robotic systems has been slow. Ultimately, the technology may prove to be of sufficient benefit to justify the increased cost, but without evidence suggesting the superiority of robotics, this remains a matter of debate at this time.

Other Emerging Technologies

Reduced-port laparoscopic surgery is one of the more recent innovations being pursued for use in the field of minimally invasive colorectal surgery. Single-incision laparoscopic surgery (SILS) is appealing as it further reduces invasiveness and has

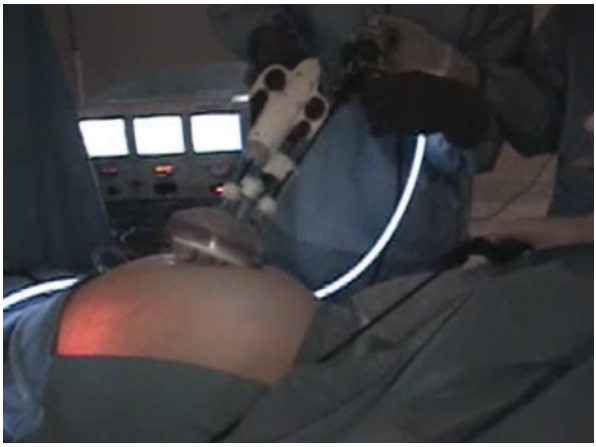

Fig. 8.5 External view of a single incision port. (Courtesy of Howard Ross, MD)

greater cosmetic benefit over conventional multi-port laparoscopy (Fig. 8.5). However, the loss of triangulation, frequent instrument-scope collisions, and operative field obstruction due to parallel instrument placement makes its application in advanced colorectal procedures difficult. There is evidence that SILS may have a role when performed for right-sided colon lesions by experienced surgeons; however, the evidence for rectal cancer is currently limited [47].

Many advances have been developed for the transanal excision of select low-grade rectal lesions. Transanal Endoscopic Microsurgery (TEM), first described in the 1980s, allows for the transanal resection through the use of specialized equipment to include an operating proctoscope, insufflator, and stereoscopic vision [48]. This technique is described in detail in another section of this main chapter. Since then, Transanal Minimally Invasive Surgery (TAMIS) has been established utilizing specially designed instruments placed through a single-port device. Considerable experience has been gained with TAMIS over recent years, and it is now a viable option for the local resection of select malignant lesions of the rectum [49]. The details of this technique are also outlined in Chap. 9 by Raskin and the notion of a Transanal TME in Chap. 10 by Lacy and colleagues. Robotic TAMIS has also been described and is a natural application of the robotic platform. However, this technique is still in the very early stages of development and data are limited [50].

Conclusions

The optimal approach for the resection of rectal cancer has yet to be determined. It is clear that minimally invasive approaches have many significant short-term advantages over open resection in the treatment of rectal cancer, but this must be considered in light of oncologic principles. Current evidence appears to support both short- and long-term oncologic equivalence of laparoscopic resection when

compared with open surgery; albeit, the evidence is not as robust as that supporting the use of MIS for colon cancer. Currently ongoing large-scale, multicenter, randomized controlled trials should more define its role. The implementation of robotic technology has the potential to address some of the shortcomings of standard laparoscopy while preserving the well-known patient benefits of MIS, however further research is needed to show clear benefit over traditional laparoscopy and to justify its increased cost. Surgeon experience is an important determinant of patient outcome and much of the favorable data supporting MIS for rectal cancer are predicated on having an adequately trained surgeon familiar with minimally invasive colorectal surgery. Therefore, appropriate training and surgeon credentialing will be an important issue moving forward as new minimally invasive techniques and technologies are developed and applied. Steep learning curves and significant cost continue to be barriers to more widespread use of minimally invasive techniques. However, as new technologies are developed and surgeon experience with these technologies increases, it is clear that MIS will continue to play an important and ever growing role in the surgical treatment of rectal cancer.

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Chapter 9
Local Excision: Indications and Techniques

Deborah S. Keller and Elizabeth R. Raskin

Introduction

The treatment for rectal cancer continues to evolve. Advances in surgical technique and chemoradiation are decreasing local recurrence and downstaging the disease enough to impact treatment plans. Surgical excision of the primary tumor remains essential for eradication of disease. Local excision is increasing in popularity for its low morbidity and excellent functional results. However, its use is limited by the inability to assess regional lymph nodes and uncertainty of oncologic outcome [1]. Questions remain on who is a candidate, if there is a need for adjuvant treatment in addition to local excision, and how to handle failures of local excision. Careful preoperative staging, patient selection, and multidisciplinary team and patient input is vital for using local excision as curative therapy in appropriate patients.

History of Rectal Cancer Treatment

Colorectal cancer is the 3rd most prevalent cancer and 3rd leading cause of cancer mortality in the United States. In 2018, an estimated 39,220 new cases of rectal cancer alone will occur in the United States (25,920 cases in men; 17,110 cases in women) [2]. Forty percent of patients diagnosed with rectal cancer present with localized disease [3]. Prior to the mid-1980s, surgery alone was advocated for all stages. Historically, these patients underwent a total mesorectal excision (TME) via

D. S. Keller
Division of Colon and Rectal Surgery, Columbia University Medical Center, New York, NY, USA

E. R. Raskin (✉)
Department of Surgery, Loma Linda University Health, Loma Linda, CA, USA

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low anterior resection (LAR) or abdominoperineal resection (APR), depending on tumor location and patient function, providing good local control and survival rates [4–6]. The importance of proper surgical technique and chemoradiation in patients with Stage 2 or higher and node positive disease then became apparent for improving outcomes, as controlled trials emerged demonstrating the benefits of surgical technique and postoperative chemoradiotherapy. The "holy plane" of surgery was defined, and performing the oncological resection along these embryological fascial planes, where all radial lymphatics in the mesorectal fascia are excised with the tumor, with adjuvant therapy was shown to decrease local recurrence rates and improve survival [4, 7–10]. These modalities became standard of care for resectable disease; however, the optimal timing for treatment modalities continued to develop. The Dutch Rectal Cancer Trial found short-term preoperative radiation therapy and TME had significantly lower rates of local recurrence compared to patients undergoing surgery alone [11]. Subsequently, the German Rectal Cancer Study (CAO/ARO/AIO 94 trial) demonstrated that preoperative chemoradiotherapy led to significantly improved rates of local recurrence, lower toxicity, and sphincter preservation than postoperative chemoradiotherapy, leading to the paradigm shift from postoperative to preoperative chemoradiotherapy [12]. Using the preoperative multimodal approach with TME, pelvic recurrence rates fell to less than 10%, with rates of pathologic complete response (pCR)- defined as no residual cancer found on histological examination of the specimen- reported in 10–30% of patients [13, 14].

The Current Gold Standard

Proctectomy with total mesorectal excision (TME) of its associated lymph node basin in the "holy plane" remains the gold standard of care in all stages of localized rectal cancer [15, 16]. Radical excision allows complete pathological staging to direct treatment and is curative for node-negative, early T-stage cancers. However, there is significant morbidity, mortality, and impact on quality of life with radical resection [17–20]. Radical resection carries a 2–3% perioperative mortality rate and 20–30% overall complication rate [19]. Additionally, long-term complications such as sexual impotence, decreased fecundity, alterations in bowel function, and the potential for a permanent ostomy can adversely affect quality of life [17–20].

Emergence of Local Excision

A trend towards less invasive surgery has emerged to address the morbidity and mortality associated with major pelvic surgery. Early-stage rectal cancers may not warrant aggressive treatment, thus advocating such sphincter-sparing approaches as

local excision (LE) [19–21]. Improved staging modalities and increased rates of pCR, have also furthered the question of the feasibility of LE for curative treatment [22]. The rates of local excision for Stage I rectal cancers have been increasing [23, 24]. A study from the National Cancer Database from 1998 to 2010 found the use of local excision steadily increased for T1 cancers ($p < 0.001$), from 39.8% in 1998 to 62.0% in 2010, while T2 LE rates rose from 12.2% to 21.4% [24].

Patient Selection

Preoperative staging is critical for proper patient selection. The preoperative staging involves physical exam, a complete colonoscopy, imaging, and histologic evaluation of the lesion. On digital rectal exam, an amenable lesion should be mobile without fixation to adjacent structures. A CT scan of the chest, abdomen, and pelvis should be performed to rule out synchronous lesions and metastatic disease. An MRI of the pelvis and/or an endorectal ultrasound can be utilized to more definitively establish T and N stage.

Local excision is appropriate for lesions localized to the bowel wall without extension beyond the muscularis propria (uTis and uT1), with favorable histopathologic features, without nodal disease, and with no evidence of distant metastatic disease. Traditional dictum states that lesions appropriate for transanal excision should be less than 4 cm in size, encompassing less than 40% of the circumference of the bowel, and within 10 cm of the anal verge [25]. However, transanal minimally invasive surgery has allowed for expansion of these criteria to include lesions higher in the rectum. Favorable histopathologic features for LE include well- to moderately-differentiated tumors, without evidence of lymphovascular or perineural invasion, and non-mucinous tumors. Tumor budding is considered a poor histopathologic feature associated with lymph node metastasis and predicative of worse survival, even after TME [26, 27]. Despite these stringent selection criteria, local excision continues to be plagued with a high recurrence rate in both T1 and T2 tumors due to a significant rate of occult locoregional metastases (20–33%) [15]. Even preoperative staging and histologic markers cannot reliably identify lymph node involvement. Thus, local resection should be used in appropriately selected, early stage patients [28].

Pathologic Staging Criteria

Pathological staging for malignant polyps uses the Haggitt and Kikuchi classifications for adenocarcinoma in pedunculated and sessile polyps, respectively [29]. In 1985, Haggitt et al. found the level of polyp invasion into the rectal wall should be the major factor determining prognosis and guiding management, and developed a

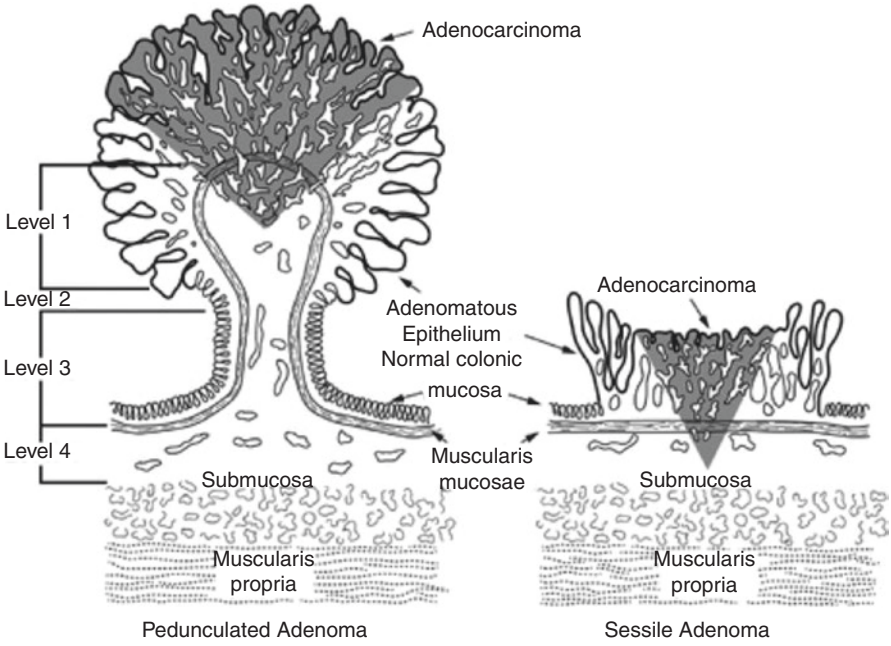

Fig. 9.1 Haggitt classification of malignant polyps. (From: Williams et al. [88])

histological classification system for pedunculated malignant polyps [30] (Fig. 9.1). With this guidance, polyps up to Level 3 can be treated safely with polypectomy or local excision, while level 4 lesions should be treated by radical resection due to increased risk of lymph node metastases [31].

Level of invasion with the Haggitt classification	
Level 0	Carcinoma in situ/intramucosal carcinoma
Level 1	Carcinoma invading through muscularis mucosa into submucosa, but limited to the head of the polyp
Level 2	Carcinoma invading the level of the neck of the adenoma
Level 3	Carcinoma invading any part of the stalk
Level 4	Carcinoma invading into the submucosa of the bowel wall below the stalk of the polyp, but above the muscularis propria

As an adjunct to Haggitt's classification, the Kikuchi classification system was developed based on depth of invasion into the submucosa (sm) [32, 33]. In this system, the submucosa is divided into three layers: sm1 lesions are limited to the upper third; sm2 represents the middle third; and sm3 lesions represent the lower third of the submucosal layer (Fig. 9.2). Lymph node metastases increase with the Kikuchi level. In pT1 tumors, the frequency of lymph node metastasis that involve the upper, middle and deep thirds of the submucosa have been reported as 2%, 8% and 23%,

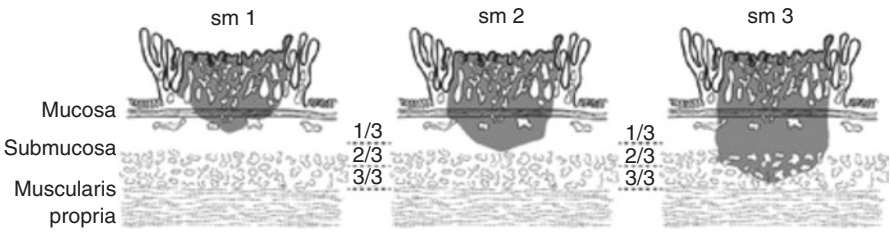

Fig. 9.2 Kukichi classification of submucosal invasion. (From: Williams et al. [88])

respectively [34]. Recurrence rates also differ significantly by sm level. In a study of 48 pT1 rectal cancer patients undergoing TEM, Morino et al. found rates of local recurrence after mean follow-up of 54.2 months were 0% in sm1 cancers and 22.7% (5/22) in sm2–3 ($p < 0.05$) [35]. Submucosal infiltration was also a significant risk factor for recurrence, with 0% in sm1, 16.7% sm2, and 30% sm3 [35]. Thus, LE has been supported for sm1 and sm2 lesions, with the acceptable risk of local recurrence and lymph node metastasis. However, with higher lymph node metastases and recurrence rates, sm3 lesions require more aggressive treatment to address the lymph node basin [36].

Advantages, Disadvantages, and Outcomes of Local Excision

Advantages of LE include lower perioperative mortality, major postoperative complications, and need for a permanent stoma, as well as improved function from a sphincter-sparing procedure [37, 38]. Local excision of appropriate rectal tumors minimizes blood loss and fluid shifts, allows for regional anesthesia over general anesthesia, and typically results in a more rapid postoperative recovery [39]. Furthermore, local excision can serve as a diagnostic purpose and bridge to radical surgery or as an option to patients whose comorbidities preclude them from tolerating radical resection [40].

There are disadvantages with local excision. The most obvious limitation is the absence of pathologic staging of nodal involvement. Treatment decisions for colorectal cancer vary based on lymph node status [27]. With this in mind, the inability to predict lymph node involvement preoperatively should give caution when performing LE. To evaluate if lymph node metastases can be predicted and potentially increase the patients eligible for LE, Blumberg et al. evaluated the T stage and other pathologic factors in radical resection patient. The authors found even in T1 tumors with no adverse pathologic features, the overall risk of undetected and untreated lymph node metastases was considerable, and the use of pathologic factors alone did not reliably preclude lymph node metastases after LE [18]. The limitations of endorectal ultrasound for accurate staging of early nodal disease paired with the predilection of lymph node micrometastases in early rectal lesions

may contribute to higher recurrence rates seen after local excision compared to those undergoing radical resection [41]. Salinas et al. found that despite indications of negative nodes, preoperative imaging with MRI and CT-scan, in addition to endorectal ultrasound, were unreliable for reading node negativity in early stage rectal cancer. In their review of 35 patients with radiographic T1N0 or T2N0 disease, 11% with T1 disease and 28% with T2 disease had positive nodes on histopathologic exam. With preoperative predictors of lymph node involvement unreliable, up to 89% of patients with T1 disease and 72% T2 disease underwent unnecessary radical resection [28]. In a systematic review, Glasgow et al. reported that no single feature reliably predicted lymph node metastases when only the primary lesion is available for evaluation in rectal cancer [27]. Thus, caution should be used when basing the treatment decision for LE on preoperative nodal factors and other variables.

With these limitations, patients undergoing local excision have a higher local recurrence rate [38–40]. While LE can be curative in early rectal cancer, approximately 20% of patients will develop local recurrence from unrecognized and unresected regional lymph node metastases [18]. In a retrospective study of 282 patients undergoing either transanal excision or radical resection for T1 rectal cancer over a 10-year period, Nash et al. found significantly higher local recurrence rates with LE compared to radical resection- 13.2% vs. 2.7% ($p = 0.001$) [40]. Madbouly et al. reviewed local recurrence, distant metastasis, results of salvage surgery, and survival in T1 low rectal cancer patients undergoing LE, and found high recurrence and low salvage rates. The 5-year recurrence was 29%, 5-year cancer-specific survival 89%, and 5-year overall survival 75%. Fourteen of 15 recurrence patients underwent salvage treatment, with a 56.2% 5-year survival rate, thus questioning the role of LE [20]. Bentram et al. had similar findings in T1 patients. They compared patients undergoing LE (n = 151) with radical surgery (n = 168) to assess patient selection, recurrence, and survival. The authors found patients who underwent LE had a three to fivefold higher risk of tumor recurrence and distant recurrences, and significantly worse recurrence-free survival ($P = 0.0001$) [17]. Mellgren et al. agreed LE might compromise overall survival in patients with rectal cancers compared with radical surgery. The authors analyzed local failures with LE compared with standard resection, finding significantly higher local recurrence rates for LE compared to radical surgery overall (28% vs. 4%), T1 (18% vs. 0), and T2 lesions (47% vs. 16%). Overall survival also was worse for those receiving local excision (69% vs. 82%), with T1 lesions (72% vs. 80%), and T2 lesions (65% vs. 81%) [42]. Based on these findings, You et al. looked at the rates and outcomes of LE compared with radical resection from the National Cancer Database for 35,179 Stage I rectal cancer patients. LE was performed more often over the study period for T1 (26.6–43.7%) and T2 (5.8–16.8%) rectal cancers. This resulted in significantly lower 30-day morbidity (5.6% LE vs. 14.6% radical resection; $P < 0.001$), but had significantly higher 5-year local recurrence rates for both T1 (12.5% vs. 6.9%) and T2 (22.1 vs. 15.1%) cancers versus standard resection, respectively [39]. In another analysis of rectal cancer from the National Cancer Data Base between 1998 and 2010, Stitzenberg et al. found positive margins were significantly more likely after LE than radical

resection excision in both the T1 and T2 lesions ($p < 0.001$) [24]. Based on these results, careful examination of the LE resection specimen should be performed, with consideration of subsequent radical resection in patients found to have T2 disease or greater disease, or high-risk features.

Survival outcomes with LE compared to formal resection for T1 and T2 patients vary in the literature, from similar to significantly worse overall and disease-free survival for Stage 1 disease [1, 24, 39, 43]. The differences in outcomes could be influenced by age, comorbidities, and with more precise methods for LE, the type of surgery [44]. A recent meta-analysis showed that while LE was associated with significantly lower 5-year overall survival (72 more deaths/1000 patients), the difference ceased in the subgroup using transanal endoscopic microsurgery (TEM)- an advanced endoscopic method [38]. In addition LE may be used more on tumors in the lower third of the rectum, which have poorer prognosis, impacting overall survival comparisons between LE and radical surgery [38]. A systematic review specifically comparing TEM with radical resection in 942 patients (10 trials) reported similar distant recurrence, overall survival (OR 0.90; 95% confidence interval 0.49, 1.66; P = 0.74) and mortality [45]. These results again emphasize the importance of surgical technique.

In sum, patients trade a higher rate of rectal cancer cure for a lower risk of morbidity and mortality [46]. As LE represents a less oncologically complete procedure with inherently higher recurrence rates [40, 46], careful preoperative patient selection and stringent postoperative surveillance is paramount.

Expanding Criteria for Local Excision with Neoadjuvant Therapy

It is accepted that LE alone is associated with a high risk of local recurrence and inferior survival compared with transabdominal rectal resection. Neoadjuvant chemoradiotherapy (CRT) is extending the indications for LE in selected patients with early-stage rectal cancer, including T2N0 patients. CRT has been shown to downstage tumor size and sterilize perirectal lymph nodes, thereby inducing a pathological complete response in up to 30% of patients [47, 48]. With this, evidence that neoadjuvant chemoradiotherapy followed by LE might be considered as an organ-preserving alternative in carefully selected patients who refuse, or are not candidates for, transabdominal resection continues to grow.

Between 1991 and 2009, Habr-Gama et al. evaluated 118 patients with low rectal cancer who received preoperative CRT; 36 (30.5%) achieved a complete cCR and 30 were followed without operation- the "Watch and Wait strategy" [49]. The authors found 80% maintained a complete response 1 year, and after 5 years, the local failure rate was 6% (n = 8); the majority of those patients had successful surgical salvage. In 2006, the authors updated analysis on 361 patients, where 99 (27%) had sustained cCR for at least 1 year [50]. The clinical T stages were unknown in 21%, T2 in 14%, T3 in 61%, and T4 in 4%, with nodal status unknown in 21%, node

negative in 57%, and node positive in 22%. In these patients, there was endoluminal recurrence in five (5%) patients, no pelvic regional recurrence, but eight (8%) patients developed metastatic disease. The 5-year disease-free survival and overall survival were 85% and 93%. While not standard of care for patients fit for formal resection, the spectacular results Habr-Gama achieved with the "Watch and Wait strategy" has spurred interest and further trials.

Looking at outcomes for LE after CRT, Lee et al. evaluated outcomes in 27 patients, finding a 5-year local disease-free survival of were 88.9%, distant metastasis-free survival of 81.1%, recurrence-free survival of 77.8%, and overall survival of 85% after a median follow-up of 81.8 months [51]. The 5-year distant metastasis-free survival, recurrence-free survival, and overall survival were significantly better for ypT0-1 compared with ypT2-3, leading the authors to conclude that LE following preoperative CRT might be an alternative treatment for highly selected patients who have achieved ypT0-1 after preoperative CRT. A pooled meta-analysis comparing patients with T3/any N stage rectal cancers undergoing radical surgery or LE after neoadjuvant CRT found comparable rates of local recurrence (OR 1.29, CI 0.72–2.31, p = 0.40), 10-year overall survival (OR 0.96, CI 0.38–2.43, p = 0.93), and 5-year disease-free survival (OR 1.04, CI 0.61–1.76, p = 0.89) [52]. Based on this data, LE post-CRT may represent a viable alternative to radical resection in select patients, but controlled studies are required to validate these results. Borstlap et al. performed a meta-analysis of pT1/pT2 rectal cancers removed by LE and followed by either adjuvant chemoradiotherapy or completion surgery found the average local recurrence rate with adjuvant CRT was 14% compared to 7% after completion TME, while distance recurrence rates were 9% in both cohorts [53]. While there were higher recurrence rates after LE and adjuvant CRT, the authors felt a reasonable approach in select patients was close follow-up and salvage mesorectal surgery, as needed. With this, a multicenter randomized trial is underway randomizing patients with an intermediate risk T1-2 rectal cancer that has been locally excised between adjuvant chemo-radiotherapy and standard completion TME; we await the results and long term outcomes [54]. Most notably, the American College of Surgeons Oncology Group (ACOSOG) Z6041 aimed to assess the efficacy and safety of neoadjuvant chemoradiation (CRT) and local excision (LE) in a multi-institutional, single-arm, open-label, non-randomized, phase 2 trial of patients with clinically staged T2N0 distal rectal cancer treated with neoadjuvant chemoradiotherapy at 26 ACOSOG institutions [47]. Eligible patients had clinical T2N0 rectal adenocarcinoma staged by endorectal ultrasound or endorectal coil MRI, measuring less than 4 cm in greatest diameter, involving less than 40% of the circumference of the rectum, located within 8 cm of the anal verge, and with an Eastern Cooperative Oncology Group performance status of at least 2. Included patients were treated with neoadjuvant capecitabine, oxaliplatin and radiation (45 Gy, followed by a boost of 5.4 Gy, for a total dose of 50.4 Gy) followed by LE 6 weeks after CRT. In the initial report, the authors found high rates of pCR (44%), tumor downstaging (64%), and negative resection margins [47]. In the long-term follow-up of 72 patients included, the 3-year disease-free survival was 86.9% [55]. While the authors state the observed 3-year disease free survival was

not as high as anticipated, CRT followed by LE might be considered as an organ-preserving alternative in carefully selected patients with T2N0 rectal cancer patients.

Salvage After Local Excision

With the increasing rates of LE, alone or in combination with chemoradiation, higher risks of disease recurrence have been demonstrated [56]. Strategies for surgically managing recurrent disease- or salvage have been described for this situation. From the earliest reports by Paty et al., low rates of survival among surgically salvaged patients (30%) is reported, with neither adjuvant radiotherapy nor salvage surgery was reliable in preventing or controlling local recurrence, and the need for postoperative intervals to span out as long as 10 years for full surveillance on LE patients [1]. In reviewing the data on 46 patients who had undergone transanal LE as definitive surgical treatment for primary rectal cancer at initial diagnosis from the University of Texas MD Anderson Cancer Center between 1993 and 2011, You et al. cautioned that failure after local excision for rectal cancer may not be salvageable [56]. Four patients (9%) had recurrence that was unsalvageable, while 40 (87%) underwent surgical salvage. After multimodality therapy in the salvage group, the R0 resection rate was 80%, sphincter preservation rate was 33%, and perioperative morbidity was 50%. Even with salvage, the 5-year overall and 3-year re-recurrence-free survival were 63% and 43%, leading the authors to conclude there is modest success in long-term disease control [56]. Bikhchandani et al. had similar conclusions in reviewing the long-term oncologic outcomes of patients that underwent salvage surgery for local recurrence after initial LE at the Mayo Clinic in Minnesota between 1997 and 2013. In the 27 patients reviewed, the sphincter-preserving rate after salvage was 33%, 5-year overall survival was 50%, and re-recurrence-free survival was 47% [57].

Failure of Local Excision

Due to the imprecise nature of the preoperative staging modalities, it is not uncommon for a preoperatively staged T1N0 rectal cancer to have a final pathological stage of T2 or T3 [58]. One option when faced with unfavorable pathology is to offer the patient immediate radical resection. Studies have reported that the oncologic outcomes in patients treated by immediate radical resection after LE for unfavorable histologic findings are comparable to that of radical surgery performed as a primary treatment [15, 58–60]. In reviewing the experience at the Mayo Clinic, Hahnloser et al. matched 52 patients that underwent radical surgery within 30 days after LE with 90 patients with a T2-3N0-1 primary as that underwent radical surgery as a control group, finding similar 5-year (79% vs. 91%) and the 10-year

survival (65% vs. 78%), respectively [61]. Failure of local excision from occult mesorectal lymph node metastases is usually treatable with salvage total mesorectal excision [15, 62]. As proctectomy may be unnecessary in a significant proportion of patients with unfavorable pathological features after LE, Perez et al. evaluated transanal endoscopic surgery (TEM) and salvage resection in unfavorable pathologic features. In 53 patients undergoing TEM following neoadjuvant CRT, 36 patients with "near" complete response to CRT (≤3 cm; ycT1-2N0) were offered TEM; none underwent immediate completion TME. The authors found salvage resection for local recurrence following CRT and TEM was associated with high rates of CRM positivity (87%) and local re-recurrence, advocating for immediate completion TME in patients with unfavorable pathological features after TEM [63].

Postoperative Surveillance

With higher recurrence rates compared to radical resection, strict surveillance is necessary after local excision for invasive rectal cancer. Per the National Comprehensive Cancer Network (NCCN) Guidelines, patients should receive a history and physical and CEA level (for T2 or greater lesions) every 3–6 months for 2 years, then every 6 months for a total of 5 years, an annual chest/abdominal/pelvic CT for 5 years, and colonoscopy in 1 year after LE [64]. With LE, proctoscopy or flexible sigmoidoscopy with EUS or MRI is also recommended to evaluate the rectal anastomosis for local recurrence every 3–6 months for the first 2 years, then every 6 months for a total of 5 y [25]. Strategies are available for serially elevated CEA levels, isolated pelvic recurrences, and documented metachronous metastases found by imaging or biopsy found during surveillance, and treatment plans should be carried out considering the guidelines, patient, and multidisciplinary team recommendations.

Techniques for Transanal Excision

Traditional Transanal Excision (TAE)

Patients may perform a full mechanical bowel preparation or enema preparation prior to the surgery. Typically, the patient is oriented either in lithotomy, lateral, or prone position, depending on the location of the tumor. Transanal excisions should be done as a full thickness resection down to perirectal fat, creating a 1-cm radial margin. The specimen should be pinned and oriented before submitting it to the pathologist to avoid enhance orientation and minimize specimen contraction from soaking in formalin. The defect in the bowel wall is subsequently closed in a

transverse manner to prevent restriction of the rectal lumen. Postoperative recovery tends to be short, with early resumption of regular diet and activity. Depending on the location of the tumor, most patients experience minimal discomfort, allowing for same-day discharge. The technique has technical and oncologic limitations. However, if final pathology is unfavorable, TAE may be used as a biopsy and bridge to formal resection.

Local recurrence rates have been reported from 4% to 57% after TAE [65]. Long-term results of TAE compared with radical surgery for T1 rectal cancer found higher rates of tumor remnants, local recurrence (12% vs. 6%, P = 0.010), inferior overall survival (70% vs. 80%; P = 0.04) and disease-free survival (64% vs. 77%; P = 0.01); however, TAE patients were older than those who had major surgery (mean 77 vs. 68 years, P < 0.001) [19].

Transanal Endoscopic Microsurgery

To address the technical limitations of conventional transanal excision, Professor Gerhard Buess developed transanal endoscopic microsurgery (TEM) in the early 1980s. Compared with conventional transanal resection, TEM provides superior exposure of rectal tumors, greater resection precision, lower morbidity and shorter hospital lengths of stay compared to radical resection [66]. Although TEM was initially used exclusively for benign lesions and as palliation for malignant tumors in high-risk patients, the indications have expanded with experience.

The procedure is performed under general anesthesia with the patient positioned to orient the lesion at the 6 o'clock position. Either the standard TEM equipment by Wolf *(Richard Wolf Medical Instruments, Chicago, Illinois*) or specialized TEO® (transanal endoscopic operation*)* proctoscope (Karl Storz, Tuttlingen, Germany) instrumentation is utilized. These systems include an operative proctoscope that attaches to the operating table via a jointed arm and has working channels for the dedicated optics and instruments.

CO2 insufflation is required to maintain endoluminal pressures between 8 and 16 mmHg. Dissection usually begins at the right lower border of the tumor, and continues continued circumferentially with a full-thickness excision down to the perirectal fat. Circumferential margins of at least 1 cm are recommended with all malignant lesions. The specimen is removed transanally, and the rectal wall defect is closed. At the end of the procedure, patency of the rectum is verified with the proctoscope [67].

TEM offers technical advantages of superior visualization with more secure closure of the defect after full-thickness excision than TAE [68]. In non-invasive and low-grade cancers, TEM offered significantly lower local recurrence rates than traditional TAE [69, 70]. TEM was also been reported to have a higher rate of negative margins than traditional TAE [70]. Compared to radical resection in Stage uT1 node negative patients, TEM had lower morbidity [68]. Despite these advantages, residual

adenomatous tissue has been reported in the surgical margins in up to 37% of TEM procedures [71, 72]. Further, unacceptably high local recurrence rates have been described- up to 26% for pT1 and 22% for pT2 lesions [73]. The 5-year malignant recurrence likelihood has been estimated at 15% for adenomas with high-grade dysplasia and 13% for cancers [72, 74].

While TEM has higher recurrence rates than radical resection, patients may undergo surgical salvage. Bach et al. found conversion to radical surgery based on adverse TEM histopathology was safe for pT1 and pT2 lesions [75]. Stipa et al. also had good long-term outcomes in Tis and T1 cancer patients who underwent a salvage operation [76]. The full-thickness en-bloc TEM specimen can also serve as a "complete biopsy," allowing for a more accurate pathological evaluation and precise disease staging. TEM can be thought of as a bridge to radical surgery.

TEM suffers from the same shortcomings as traditional TAE in being unable to adequately stage the pelvis. Using the same post-operative surveillance schedule as traditional transanal excision, most recurrences can be detected early enough to allow for salvage surgery. Studies generally support use of TEM alone for Tis and favorable T1 lesions. In higher-grade T2 tumors or unfavorable T1 or T2 tumors, neoadjuvant or adjuvant treatment can be used with subsequent LE [77, 78]. For more advanced lesions, TEM is not appropriate for patients undergoing surgery with curative intent, and should be offered just for palliation or medically patients unable to tolerate more extensive surgery [73, 77, 78]. The technique is also not yet widely utilized because of the costly specialized equipment, the distinct technical aspects of the approach, stringent patient selection criteria, and absence of an adequate lymphadenectomy [66].

Transanal Minimally Invasive Surgery

TransAnal Minimally Invasive Surgery (TAMIS) is another tool for local excision (Fig. 9.3). TAMIS, a hybrid between TEM and single-port laparoscopy, is performed placing a single-incision laparoscopic surgery port into the anal canal, establishing pneumorectum, and then using standard laparoscopic instruments for the transanal excision [79]. TAMIS has been shown to be safe and feasible for selected, early-stage malignancies of the mid and distal rectum [80]. By utilizing a disposable platform and standard laparoscopic instrumentation, TAMIS has been shown to be a less costly alternative to TEM [79]. In reviewing their initial 50 patients (25 benign neoplasms, 23 malignant lesions, and 2 neuroendocrine tumors) at an average distance of 8.1 cm from the anal verge, Albert et al. completely excised 48, with only 2 fragmented specimens (4%); all specimens had grossly negative margins, and only 3 (6%) had microscopically positive margins on final pathology [80]. Their average length of stay of 0.6 days, short-term complications occurred in 3 patients (6%), and there were no long-term complications at a median follow-up of 20 months. Long-term follow-up revealed an acceptable 4% recurrence rate [80].

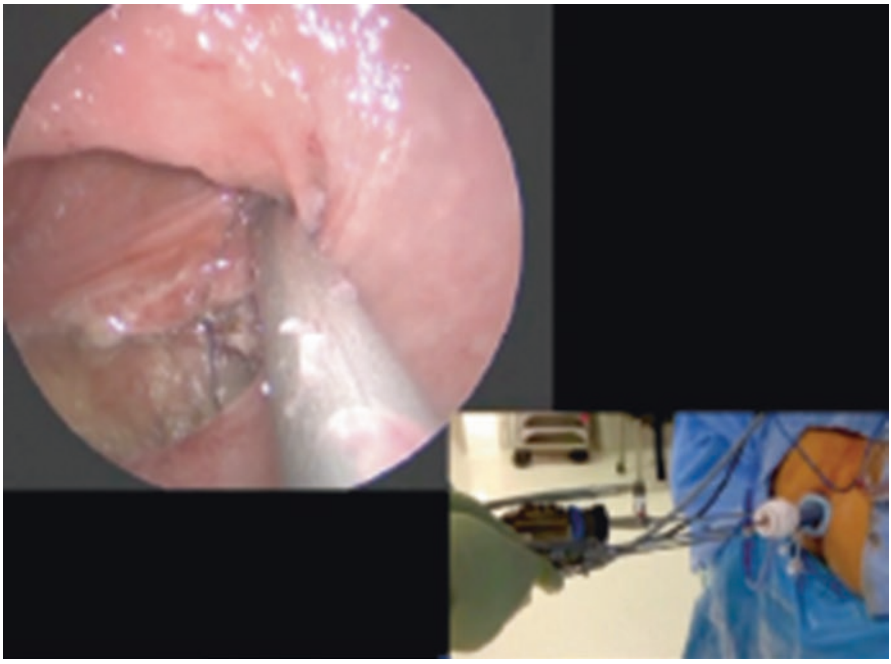

Fig. 9.3 TAMIS excision of a T1N0 rectal cancer

Robotic Transanal Endoscopic Microsurgery

With wristed instrumentation and 3-D optics, the *da Vinci* robotic surgical system has been shown to enhance depth perception and visualization in deep and narrow spaces like the pelvis and oropharynx [81–83]. Hypothesizing that the perceived advantages of the *da Vinci* robotic surgical system would apply to transanal surgery, Atallah et al. described the first applications of the surgical robot for transanal microsurgery in both cadaveric and live patient models [84, 85]. Feasible and oncologically sound excisions have been described utilizing the *da Vinci* system with both the Gelpoint platform and the transanal glove port method [86, 87]. Lithotomy, prone, and lateral positions have been described for transanal robotic surgery, although ideal patient positioning has not been determined given the limited experience with this technique. Most reports describe using three robotic trocars (8 mm) for the scope (5 mm) and two wristed instruments. The instruments are typically crossed at the level of the circular anal retractor and then reassigned on the surgeon console to address the handedness of the instruments. An assistant port (5 mm) can facilitate the use of a laparoscopic suction device for smoke evacuation. Absorbable sutures and barbed sutures have been used to close the full-thickness defects. Although early in its development, robotic transanal surgery has yet to demonstrate significant advantages over TEM and non-robotic TAMIS as the increased cost of this approach has been criticized.

Conclusions

The treatment of early stage rectal cancer is in flux. While radical resection with total mesorectal excision (TME) remains the gold standard of care in all localized stages, rates of local excision- with and without further therapy- have been increasing. New tools and technologies for local excision are extending the capabilities of the technique for treatment of early stage and benign low rectal lesions. Local excision is associated with significantly lower morbidity and mortality than formal resection. However, less invasive, sphincter-sparing procedures may not provide complete oncologic treatment. Careful patient selection is necessary to identify patients who may benefit from local excision without an elevated risk of local metastasis or recurrence. Following local excision, stringent follow up is imperative for surveillance and early detection of recurrence.

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Chapter 10
Reverse TME: The "Bottom-UP" Approach to Low Rectal Cancer

Maria Clara Arroyave, F. Borja de Lacy, and Antonio M. Lacy

Introduction

Colorectal cancer is the third most common type of cancer diagnosed in the United States, and with rectal cancer accounting for approximately the 30% of the cases. In 2016, the American Cancer Society estimated almost 40,000 new rectal cancer cases, the majority undergoing surgery – a surgery that has traditionally been difficult, especially in cases of obesity, males and those with a narrow pelvis. The oncologic cornerstone of this surgery is the removal of the mesorectum as an intact specimen *en-bloc* with a margin-free tumour. Systematic adherence to this principle has been proven to prolong survival and reduce locoregional recurrence.

In light of the importance of sphincter-preservation as a surrogate marker of quality, a new approach to resection of the rectum has developed: transanal total mesorectal excision (taTME). This technique aims to improve the quality of the TME especially in mid and low rectal adenocarcinoma, in order to enhance cancer-specific survival.

The first case reported in the literature was performed in Barcelona [1], with very good results, and giving credence to its potential benefits. Several groups worldwide have adopted taTME to their standard clinical practice. Looking back, people who made the development of this technique possible include Gerhard Buess, who implemented transanal endoscopic microsurgery (TEM) in 1983, a valuable technique that allowed local endoscopic excision of lesions not amenable to conventional transanal resection with a Parks retractor. He performed the first local excision

M. C. Arroyave
Department of Surgical Oncology, AIS Channel, Clinica Somer, Rionegro, Colombia

F. B. de Lacy
Department of Gastrointestinal Surgery, ICMDM, AIS Channel, Hospital Clínic, Barcelona, Spain

A. M. Lacy (✉)
Department of Gastrointestinal Surgery, ICMDM, IDIBAPS, CIBEREHD, AIS Channel, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain
e-mail: alacy@clinic.cat

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of a rectal adenoma using a rigid rectoscope [2], and planted the seed for future minimally invasive developments. In 1984, Gerald J. Marks developed the transanal abdominal transanal proctosigmoidectomy with coloanal anastomosis (TATA) [3]. This technique, with a full thickness incision at the level of the dentate line, accounted for an enlargement of the role of sphincter-saving surgery. Mark H. Whiteford first performed a NOTES transanal endoscopic rectosigmoid resection in a cadaver, demonstrating that an oncological resection and anastomosis was feasible [4]. Finally, Sam Atallah introduced the concept of transanal minimally invasive surgery (TAMIS). He described the use of a single-port and laparoscopic instruments for local excision of adenomas and pT1 adenocarcinomas [5]. Without their contributions, taTME would probably not be what it is today.

Indications for TA TME

Rectal cancer is the main indication for transanal rectal resection. When radical resection is needed, TME is the oncological rule that has remained valid for the last 30 years since its description by Heald [6]. Nevertheless, the optimal approach to TME is still a matter of debate. Large randomised controlled studies, including the Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASSIC), the Comparison of Open versus Laparoscopic Surgery for Mid or Low Rectal Cancer after Neoadjuvant Chemoradiotherapy (COREAN) and the COlorectal cancer Laparoscopic or Open Resection (COLOR II) trials, reported less postoperative pain, decreased length of hospital stay, and faster return of bowel function, with similar oncologic outcomes when comparing open versus laparoscopic TME [7–10]. However, longer operative times, a steep learning curve and minimal impact on functional outcomes have prevented wide adoption of laparoscopic TME. Moreover, although pelvic dissection seems to be easier with laparoscopic surgery when compared to laparotomy, there still exist difficulties in proper manipulation and dissection in such a limited space. These problems have inspired the development of new techniques, such as taTME. The “bottom-up” approach has become an important tool to expand the role of minimally invasive surgery in rectal cancer, while improving the clinical outcomes.

The main indication of taTME is mid and low-rectal cancer. Distal rectal dissection is difficult when it is performed by conventional laparoscopy, with the level of transection not being controlled directly, but based on preoperative proctoscopy or digital rectal examination. Moreover, multiple stapler firings are sometimes warranted, which has been associated with an increased risk of anastomotic leakage [11]. TaTME allows for direct vision of the distal rectal margin. This procedure, together with the possibility of an intersphincteric resection (ISR) for low tumours, allow for a sphincter-sparing procedure in patients that otherwise would be candidates for an abdominoperineal resection (APR). A partial ISR is indicated for tumours less than 1 cm from the anorectal ring and a total ISR is mandatory for tumours invading the internal sphincter, only if negative margins can be achieved.

ISR has shown similar oncological outcomes to APR in multiple series [12–14], although functional results are expected to be inferior to those of low anterior resection and therefore should be reserved for patients with adequate preoperative sphincter function and continence. After development of taTME, APR is indicated only in patients with involvement of the external sphincter or with impaired preoperative functional tests. Careful and frank information should be given to the patient before choosing ISR versus APR.

For high rectal cancer the current indications are obesity, narrow pelvis, bulky large tumours and patients with previous pelvic surgeries or radiotherapy. For large T4 tumours when en-bloc resections are needed, taTME allows for a two-plane concomitant visualisation of structures, making complex dissections more suitable and safe. It is feasible to perform a concurrent en-bloc prostatectomy, partial cystectomy, hysterectomy or salpingo-oophorectomy.

Ulcerative colitis is another indication for transanal proctectomy, allowing for direct vision of the involved mucosa and the appropriate election of the section place. In patients treated with restorative proctocolectomy and ileal pouch-anal anastomosis, acceptable outcomes have been reported [15]. Transanal surgery also encompasses local resection therapies. In other words, for benign rectal lesions and carefully selected T1 tumours, TEM or TAMIS should be considered. Other emerging indications for the transanal approach are short stump Hartmann reversal [16] and redo surgery, either early for postoperative anastomotic bleeding or anastomotic dehiscence, or late for chronic presacral sinus, fistulae, and stenosis [17]. Nevertheless, studies with larger sample size are needed.

Surgical Technique

TaTME is a surgical procedure achieved by two accesses: the abdominal and the transanal one. They can be performed consecutively (one-team approach) or simultaneously (two-teams approach, what we have named the “Cecil approach”). After more than 300 cases performed with the Cecil approach, we recommend it for its shorter operative time and visualisation of the surgical plane from two points of view. Collaboration of the two teams for traction and countertraction is a valuable feature of this technique.

If only one team is available, our recommendation is to start in the abdominal field, stopping the dissection just before opening the peritoneal reflection and continue with the transanal field afterwards. Retropneumoperitoneum, which occurs when only pneumorectum is applied, makes the abdominal dissection harder by distorting the retroperitoneal space.

Preoperative Setting

Demarcation of potential stoma sites by an enterostomal therapist, a trained nurse or a surgeon is highly recommended.

Currently oral antibiotics plus mechanical bowel preparation the day before surgery is recommended. Intravenous antibiotic prophylaxis against aerobic and anaerobic bacteria should be given 1 h before skin incision in order to decrease the risk of surgical site infections.

Sequential compression devices should be activated prior to the induction of general anaesthesia. It is important to achieve a deep neuromuscular blockade in order to get appropriate rectal distension and pneumoperitoneum. The patient is placed in the modified-lithotomy position with adjustable stirrups and in a steep Trendelenburg position. A Foley catheter is inserted using aseptic technique, and the rectum is irrigated with both saline and a cytocidal solution such as povidone iodine (Fig. 10.1).

For the two-teams approach, each team must be completed with a principal surgeon, an assistant and a scrub nurse (See Fig. 10.2). Two regular laparoscopic instrumental sets and complete laparoscopy units are needed with 30-degree scope for the abdominal team. For the transanal team, authors recommend the use of a 3D scope with flexible tip and a continuous insufflator with smoke evacuation in order to achieve a better depth perception, and proper hand-eye coordination.

Anatomic Landmarks

The pelvic cavity is a narrow space confined in an osseous and rigid case containing intestinal, urologic, gynecologic, vascular, and neural structures. As down-to-up rectal dissection is started from inside the rectal walls, there is no initial view of surrounding structures. Complete awareness of the location of these structures is mandatory in order to avoid inadvertant injuries (See Fig. 10.3). Particular care must be taken when dealing with previously irradiated patients, because the

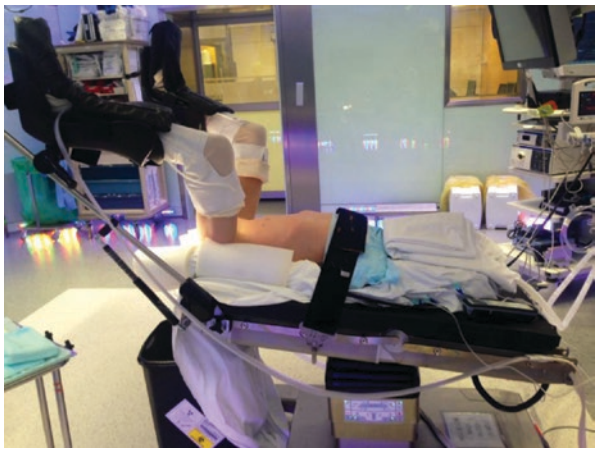

Fig. 10.1 Patient position for taTME

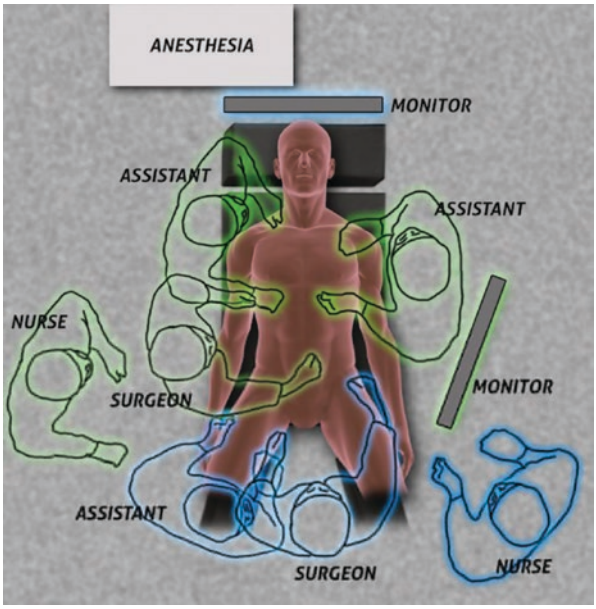

Fig. 10.2 Two-teams distribution
Blue: Transanal Team
Green: Transabdominal Team

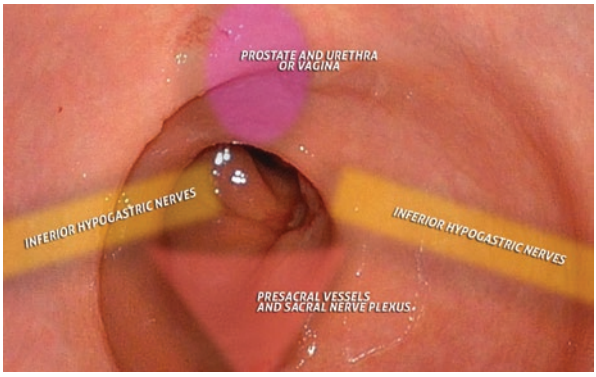

Fig. 10.3 Schematic location of anatomical structures

abnormal consistency of fibrotic tissues makes dissection more challenging. Relations to take into consideration are as follows:

- Anteriorly, the prostate and urethra in males and the posterior vaginal wall in females.
- Posteriorly, the coccyx and presacral vessels,

Laterally, the ischiorectal fossa contains fat and the inferior rectal vessels and nerves. Autonomic nerve lesions result in impotence, bladder dysfunction and retrograde ejaculation, so care must be taken to preserve these structures. Radial dissection must be kept medial to the Denonvillier's fascia anterolaterally to avoid any lesion to the lymphovascular bundles.

Technical Aspects

Transabdominal Part

The transabdominal part is initiated with 12–15 mmHg pneumoperitoneum and insertion of 4 laparoscopic ports: a 10 or 12 mm port above the umbilicus, and 5-mm ports in the left and right flank, as well as in the right iliac fossa (See Fig. 10.4). The distal sigmoid is temporarily clamped while the transanal team performs the purse-string suture to avoid colon distension. Once the purse-string is made, each team works simultaneously. For cancer resections, a medial to lateral approach is advised. Division of the inferior mesenteric artery must be performed 1 cm away from its origin from the aorta to avoid hypogastric nerve damage, following the oncological principles to completely excise the mesentery and associated lymph nodes that run alongside the vascular arcade. For this maneuver, traction is applied to the inferior mesenteric vessels and the peritoneum is opened with electrocautery allowing pneumoperitoneum to expose the avascular plane. Ligation is performed with a vessel sealing device, a vascular stapler or applying regular clips after proper identification of the left ureter to avoid inadvertent injuries (Fig. 10.5). At the level of the inferior border of the pancreas, the inferior mesenteric vein is visualised and ligated in the same fashion. Descending colon dissection is finished by taking down the Toldt's Fascia.

Rectal dissection is started following the posterior avascular plane in order to include the mesorectum in the resection. Circumferential dissection is continued to the anterior plane preserving Denonvillier's fascia until closeness with the transanal team is perceived and the "rendezvous" is achieved. At this moment, both

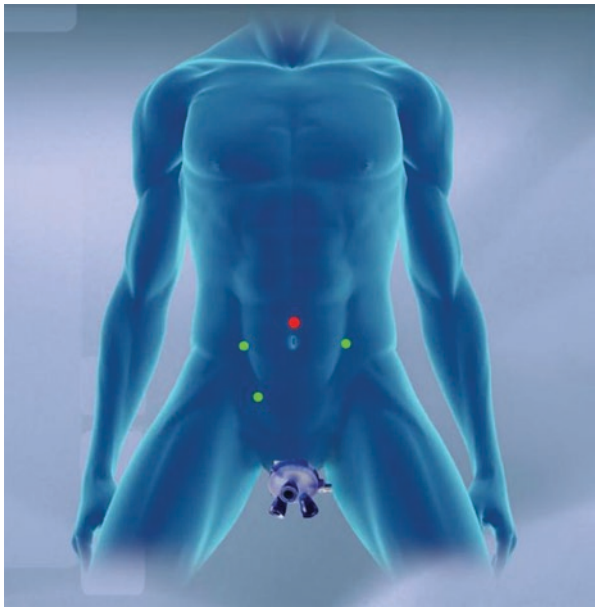

Fig. 10.4 Trocar placement

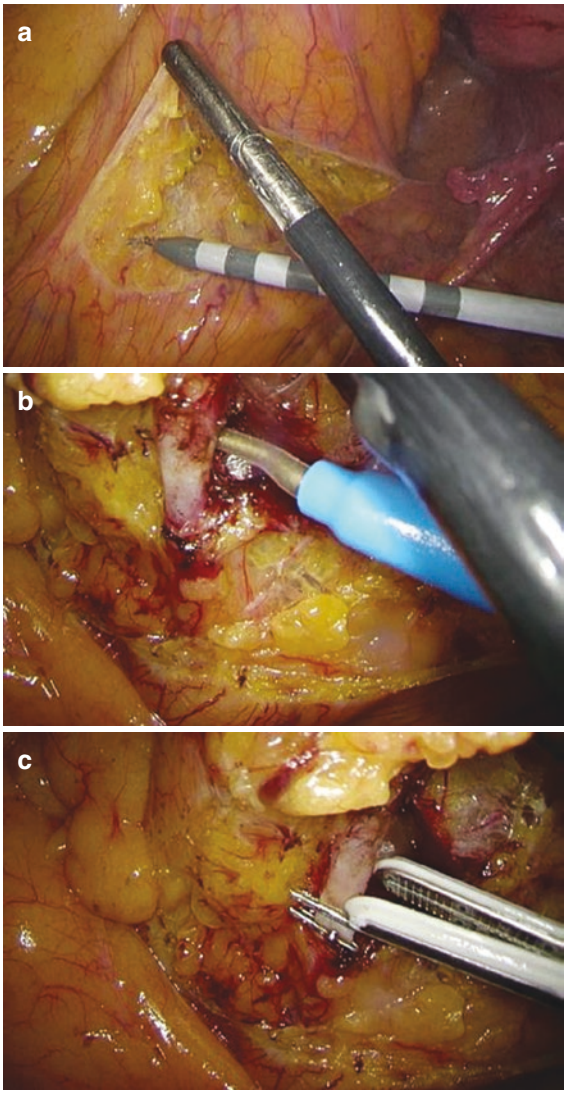

Fig. 10.5 Vascular control. (**a**) Peritoneum incision. (**b**) IMA dissection. (**c**) IMA ligation

insufflators must be set at the same pressure. Routine mobilisation of splenic flexure is not recommended unless tension in the anastomosis is anticipated, as this maneuver risks splenic bleeding, colonic ischemia or rotation. When it is required, an extra 5 mm port is inserted in the epigastrium.

Transanal Phase

A self-retaining retractor is used to open the anus and clearly identify the dentate line. Dilators are used when needed to allow a safe introduction of the transanal platform in an atraumatic way. We recommend a flexible single port device, with

wide trocar insertion in an inverted triangle shape with the scope at the lower trocar and the surgeon's instruments in both sides for maximal maneuverability.

After clamping the distal sigmoid, pneumorectum is initiated for a target pressure of 12–15 mmHg. Our recommendation is to maintain transanal pressure higher than the abdominal until the "rendezvous" moment, to ensure proper rectal distention.

The transanal team starts the procedure performing an 0 polypropylene or polydioxanone (26-mm rounded needle) purse-string distal to the tumour, with the intention of leaving this on the specimen side of the rectum, in order to close the rectal lumen. It should be fashioned at the same distance from the device in the entire circumference, with inclusion of the same amount of tissue in each bite and avoiding the incorporation of surrounding structures such as the vagina. It must be durable and air-tight to avoid contamination and tumour spillage during the procedure. The purse-string knot is either tied by hand, after removal of the transanal platform cap, or secured with a pre-formed auto-blocking knot. Flushing of the rectal stump with iodine solution is recommended to wash out any free-floating cancerous cells.

If an ISR is indicated, the dissection is started manually with conventional instruments before the device introduction. The purse-string is made after completing the initial dissection, either manually or laparoscopically. Then, the single port device is introduced.

It is useful to mark the dissection line by scoring the rectal mucosa with an electric hook just distal to the mucosal folds created by the rectal closure. This step ensures cutting at the same distance from the purse-string in the entire circumference. Full thickness and perpendicular transection of the rectal wall is initiated, taking special care to perform a 360-degree dissection proceeding deeper (See Fig. 10.6).

The mesorectal fascia should be reached circumferentially, and then a sharp upward dissection can be started, avoiding a cone shape to ensure completeness of the mesorectum. Awareness of the distance to the suture is important to avoid cutting it. At this point pneumodissection will facilitate identification of the presacral space and rectovaginal or rectoprostatic plane. When dissecting posteriorly the sacral natural curve must be remembered. The endopelvic fascia should be avoided,

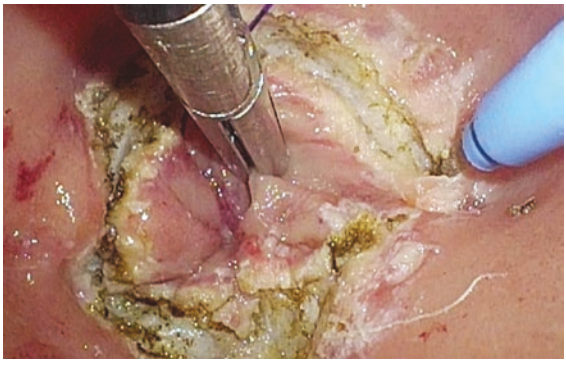

Fig. 10.6 Full thickness, 360-degree rectal wall dissection

as it is easy to encounter an areolar plane and confuse it with the true "holy plane" (See Fig. 10.7). On the anterior side, the mesorectum fat is a lot thinner and care must be taken to not penetrate Denonvillier's fascia. Digital examination of the vagina helps in the dissection of the anterior plane (See Fig. 10.8).

Lateral planes are more difficult to identify, so it is useful to follow the avascular plane from a zone where is already dissected. Going too lateral may cause significant bleeding or damage to surrounding structures.

Most of the dissection can be achieved with the electrical hook, following one of the principles of TME (sharp dissection). However, hemostasis may require the use of a bipolar forceps. Tissue exposure during dissection is better achieved by pushing the specimen into the abdomen with the surgeon's free hand, rather than pulling it through the anus.

After the "rendezvous", the two teams continue working together until the rectum and sigmoid are completely free (See Fig. 10.9). The specimen is extracted transabdominally in case of bulky tumours or a narrow pelvis, or transanally in the remainder. For transabdominal extraction a Pfannenstiel incision is preferred.

Recently, we have added indocyanine green (ICG)-induced fluorescence angiography to our clinical practice. Intraoperative assessment of anastomotic perfusion has been shown to be a safe and feasible tool to evaluate colorectal anastomoses

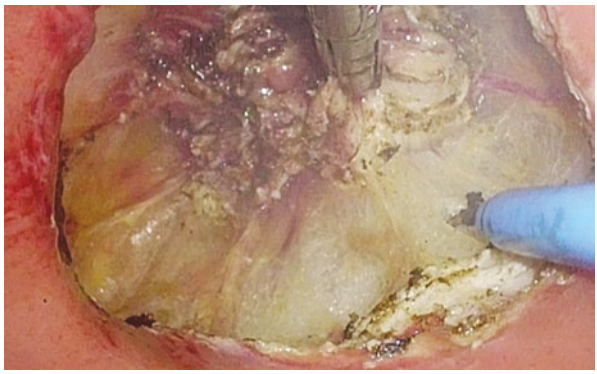

Fig. 10.7 Posterior dissection

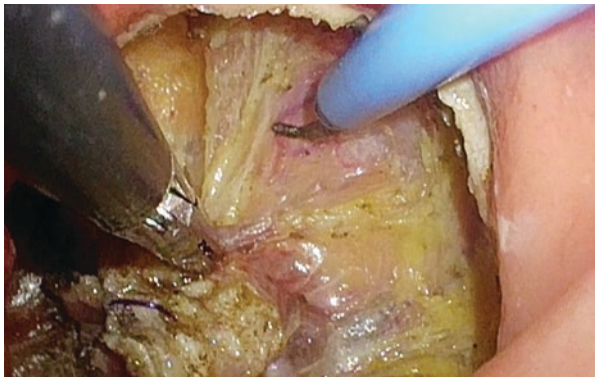

Fig. 10.8 Anterior dissection

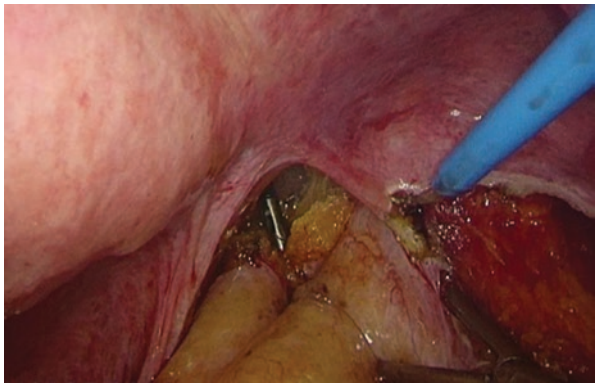

Fig. 10.9 Two teams working simultaneously (abdominal view)

[18]. Moreover, it might be associated with a decreased rate of anastomotic leak. Before transecting the specimen, we routinely check the viability of the proximal colon with fluorescence imaging after injecting ICG. With the limited experience noted, in a few cases the transection point and planned site of anastomosis was altered. We firmly believe that fluorescence with ICG in colorectal surgery will become important in the next years.

Anastomosis

After extraction of the specimen, either a hand-sewn coloanal or a stapled side-to-end or an end-to-end anastomosis is performed (See Fig. 10.10). Some groups perform colonic J pouch for ultra low anastomosis because anorectal function is thought to be improved, although there is no strong evidence supporting this technique in a long-term basis.

For the stapled technique, a continuous purse-string suture must be made with 2-0 polydioxanone in the open distal rectal stump to close the rectal wall around the stapler. The knot will be tied later around the connected anvil and the circular stapler. Anastomosis is made with a circular 33-mm diameter stapler with 4.8-mm staples, although in a few cases we might use smaller diameter devices (31 or even 28-mm). A hemorrhoidopexy stapler is preferred because of its longer spike and wider tissue involvement.

After firing, the transanal platform is reinserted to verify the anastomosis for bleeding and completeness. Air leaks must be ruled out by direct inspection of both abdominal and transanal teams. Additional stitches can be placed if considered necessary.

For a side-to-end hand-sewn technique, four reference stitches are made to the distal rectal stump and then passed through the proximal colon wall after creating a colotomy in the antimesentric border. The surgeon ensures that the colon is properly positioned without tension or twisting. An anastomosis is completed with simple stitches of 3-0 polyglycolic acid.

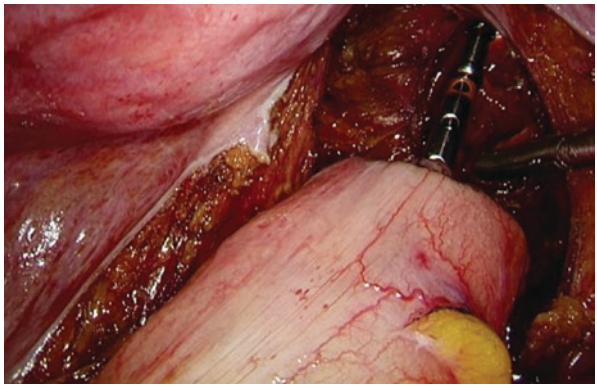

Fig. 10.10 Stapled end-to-end anastomosis

The abdominal cavity is inspected for proper hemostasis and a diverting ileostomy is made in high risk patients: previously irradiated, coloanal anastomosis, obese or with other risk factors. A closed-suction drainage is placed in the pelvis. A soft rectal tube is placed to lower intraluminal pressure.

Complications

TaTME is a technique with an enormous potential. However, new approaches carry new anatomical landmarks, with an increased risk of morbidity, especially in the beginning of the learning curve. TaTME is a complex surgery, and different structures can be damaged if dissection is inappropriate. Serious complications not documented in open or laparoscopic TME have been reported, such as urethral injuries in males [19]. If the lateral dissection is too wide, the pelvic side wall and its neurovascular structures such as the pelvic plexus and the hypogastric nerves are at risk. Posteriorly, damage to the presacral venous plexus can induce haemorrhage, although it is usually solved with local pressure or using energy devices.

In the first systematic review of taTME [20], with a pooled sample size of more than 500 patients, the overall perioperative morbidity rate was 35% and the anastomotic leak rate was 6.1%. This is consistent with rates reported for open and laparoscopic TME, of approximately 8–10% [9]. Whether or not this approach is associated with an improved anastomotic leak rate, especially in centres of excellence, needs further investigation.

Concern exists about pelvic abscess formation. Velthius et al. [21] reported an increased abdominal bacterial contamination during taTME, raising the risk of developing infectious complications. This is the reason why we advocate for flushing the lumen after closing the rectal stump with the purse-string suture, to potentially prevent spillage of tumor cells and bacteria. We also recommend leaving a pelvic drain for the first 24–48 h, in order to suction a possible hematoma that might get infected.

As in many other colorectal surgeries, there are common complications that have already been reported: some examples are urinary retention, ileus, haemorrhage of the anastomosis – which can be treated with stitches also by a transanal approach –, increased ileostomy output or surgical site infections. Their frequency compares to what has been published from laparoscopic TME.

Outcomes

Oncology

Oncological outcomes are expected to be the main strength of the technique. Since Richard J. Heald demonstrated that a well-performed TME is associated with improved disease-free survival, this quality of the resection has become an indicator of surgical accuracy and oncological safety. Completeness of the mesorectum, together with negative circumferential resection margin (CRM) and distal resection margin (DRM) are the three pillars.

Following the Quirke grading system [22], completeness of the mesorectum rate has been reported as 88–90%, while "near completeness" rate has been 6–7% [20]. Similis et al. reported a CRM negativity rate of 95% (considering it negative when distance between tumor cells and mesorectal visceral fascia was ≥1 mm). DRM was negative in 99.7%.

Up until now, with a follow-up of 15–29 months, locoregional recurrence rates range from 1.7% to 3% [19, 23–25]. Nevertheless, we still have to wait for the mid and long-term data in order to evaluate the oncological safety of taTME. With longer follow-up and more high-quality trials, we will be able to certify if taTME is similar or even superior to laparoscopic TME in terms of cancer-related survival.

Functional Results

The effect of taTME on postoperative continence still needs to be investigated. Some groups think that the transanal use of a single port may have an effect on the anal sphincter. There are no high-quality reports yet, but a pilot study based on Wexner score showed good results, with a median score of 3 at 6 months after the operation [26]. Tuech et al. [23] reported the outcomes of 56 consecutive patients treated of low rectal cancer and with coloanal anastomosis. After 1 year, the median Wexner score was 4, although three patients required a colostomy due to severe faecal incontinence. Twenty-eight percent of the patients complained of stool fragmentation and difficult evacuation.

In trained hands, taTME provides an improved and easier pelvic visualization. One of the main advantages is the sparing of the autonomic nerves, which in theory would be associated with a decreased urinary and sexual dysfunction incidence. Nevertheless, this needs further investigation.

Future Directions

Total Transanal Approach

Total transanal approach or ¨pure NOTES” have been published in a limited number of cases with limited data to find potential benefits [27–29]. Scarless surgery is to date a major motivator for minimally invasive surgery, with the advantage of no abdominal wall disruption, minimized risk of acute or late wound complications, port cancer seeding, postoperative pain and recovery time.

We consider this is a very interesting approach that would probably undergo further development once the current technique achieves consolidation and surgeons overcome the learning curve. Additional improvements are needed in materials and equipment to make this approach safer and more feasible.

Robotics

In the last decade, neoadjuvant chemoradiation therapy has become the standard of care for locally advanced mid and low rectal adenocarcinoma. Nevertheless, surgery remains the only curative treatment, with TME being the keystone. TaTME could be associated with a better rate of complete TME. However, rectal dissection requires precision and is difficult even in experienced hands.

Robotics became popular due to enhanced dexterity, reduced tremor, improved ergonomics and a stable and magnified camera view. Focusing on rectal cancer, several authors think that the use of robotic surgery could facilitate an easier dissection and decreased conversion rate, although this is still a matter of debate and is being investigated [30]. There have been some reports of robotic TME, either from above or from below [31, 32], proving its feasibility and safety. In theory, both robotic dissection and taTME might be associated with an improved quality of specimens. Authors are starting to predict satisfying results of the mixture of both techniques. In the future, perhaps with new robotic systems adapted to a transanal approach, and with decreased costs, Robotic Assisted Transanal Surgery for Total Mesorectal Excision (RATS-TME) [33] might play a relevant role in rectal cancer patients.

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Chapter 11
Watch and Wait in Rectal Cancer Patients with Clinical Complete Response to Neoadjuvant Therapy: The American Viewpoint

Felipe Quezada-Díaz, Tarik Sammour, J. Joshua Smith, and Y. Nancy You

Introduction

Surgery is the mainstay therapy for rectal cancer. Currently, standard of care includes neoadjuvant and adjuvant treatments for stage II (T3-4, node-negative disease with tumor penetration through the muscle wall) or stage III (node- positive disease without distant metastasis) due to the relatively high risk of locoregional and distant relapse [1]. However, over the past several years, the management algorithm of rectal cancer has become more complex. With the realization that a selected subset of rectal cancers can completely regress after neoadjuvant therapy (NAT), the concept of organ preservation in the context of an apparent clinical complete response has emerged, coupled with the advent of a watch and wait paradigm as well as the concepts of total neoadjuvant therapy (TNT) or treatment intensification programs.

Classic principles for surgical resection of rectal cancer with curative intent involve total mesorectal excision (TME) with adequate regional lymphadenectomy. Sphincter- preservation is performed whenever adequate tumor clearance of distal and radial margins from the anal sphincter and the levator muscles can be

F. Quezada-Díaz
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

T. Sammour
Colorectal Unit, Royal Adelaide Hospital, University of Adelaide, Adelaide, SA, Australia

J. Joshua Smith
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Department of Surgery, Weill Cornell Medical College, New York, NY, USA

Y. Nancy You (✉)
Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: ynyou@mdanderson.org

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achieved [2]. While open surgery has been the standard of care, a variety of minimal-access operations utilizing laparoscopic, robotic, and transanal access have become more common in practice. Nevertheless, regardless of the approach to resection, surgery is associated with the potential for significant complications including anastomotic leak, pelvic sepsis, ureteric injury, as well as the potential for permanent colostomy in some cases. In addition, rectal surgery is associated with a high frequency of bowel, sexual and genitourinary dysfunction that directly affects the quality of life of patients [3, 4]. Therefore, there is great interest in strategies that may spare the patients of risk of surgical resection.

The selective use of a non-operative management or watch-and-wait (WW) strategy in the setting of rectal cancers treated with preoperative chemotherapy and radiation was first reported by Habr Gama et al. [5] but has gained significant attention over the past two decades. The aim of this chapter is to discuss the rationale, limitations, and evidence for a WW strategy in rectal cancer, with additional discussion on future prospects.

Neoadjuvant Therapy (NAT) for Rectal Cancer

For patients with locally advanced rectal cancer (AJCC TNM clinical stage II and III), the standard of practice in the United States includes NAT. On the backbone of TME as the gold standard surgical treatment for rectal cancer [6], the Dutch TME trial showed significant reduction in local recurrence when patients received short-course preoperative radiotherapy (5×5Gy) versus TME alone [7]. Additional trials showed the addition of concurrent chemotherapy yielded better local control when compared with radiotherapy alone [8, 9]. Finally, the German Rectal Cancer Group demonstrated a superiority of a preoperative neoadjuvant long-course chemoradiation strategy when compared with postoperative chemoradiation and showed improved local control and a higher rate of sphincter preserving surgery [10].

The long-course strategy described as radiotherapy administered during a 5–6 week period with concomitant chemotherapeutic agents and a 6–10 week period of rest before proctectomy, provided a space for a period of observation that allows the regression of the tumor. This conduct offers considerable advantages for the surgeon in terms of free tumor surgical margins and more opportunities to achieve a restoration of normal colonic transit in low rectal tumors. “Short-course” RT modality therapy has demonstrated similar oncological outcomes when compared to long-course chemoradiation [11]. Tumor regression is also observed, if the surgery is delayed between 4 and 8 weeks, as is shown by more recent trials [12]. A National Cancer Database analysis including all stage II and III rectal cancer patients undergoing neoadjuvant chemoradiation showed that any surgery interval longer than 8 weeks had higher odds of pathological complete response (pCR) (odd ratio 1.12, 95% CI 1.01 to 1.25) [13].

Definitions of Clinical and Pathological Response

Tumor regression after NAT has been widely accepted as a predictor of long-term oncological outcomes in rectal cancer [14]. Indeed, pathological staging found at resection after NAT is more predictive of outcome than initial clinical staging [14]. When macroscopic tumor is seen after NAT, the clinical response to NAT is deemed as "incomplete" (incomplete response: IR) and proctectomy with TME is the treatment of choice. However, approximately 17% of surgical specimens show complete absence of residual tumor cells at either the primary tumor site or the nodal basin after NAT, defined as pCR or with very few isolated tumor cells (near-complete pathological response) [15].

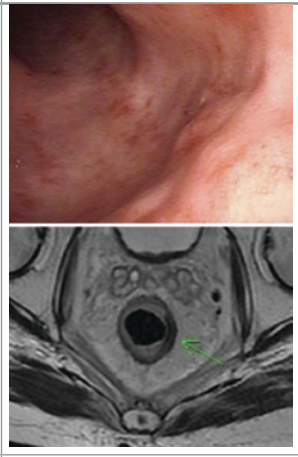
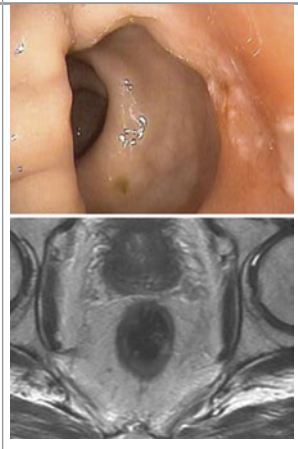
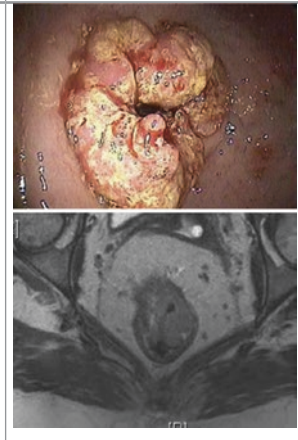
This definition must not be confused with that of an apparent **clinical** complete response (cCR), which is defined as the absence of clinically detectable macroscopic tumor. Tools and methods for clinical detection of macroscopic tumor have continued to evolve. Almost 50% of patients after neoadjuvant chemoradiation for rectal cancer experience a cCR [16], indicating that cCR does not necessarily correlate with histological pCR. In addition, a residual ulcer may be seen macroscopically in patients who may eventually go on to have pCR with time, especially when the visible ulceration represents fibrosis only [17]. The current challenge is thus to accurately select the patients with an apparent cCR, based on clinical assessment, who would be found to have a pCR if they were to undergo resection, in order to correctly identify those would-be candidates for a WW strategy without compromising oncologic safety.

Habr Gama et al. defined cCR as mucosal integrity with only whitening or telangiectasia and subtle loss of rectal wall pliability due to scarring during proctoscope insufflation [18]. In a retrospective study, the sensitivity and specificity to predict pCR using this definition was 26% and 96%, respectively [17] and in the setting of a prospective phase 2 trial, sensitivity and specificity was 85% and 67%, respectively [19].

Improved standardization of clinical assessment criteria is needed. While stricter criteria will restrict the number of eligible patients and may increase the accuracy of patient selection for the WW strategy, more liberal criteria may risk potentially worse oncological outcomes. In addition, there is an intermediate group of patients with near-complete clinical response, demonstrating a significant tumor regression but who fall short of achieving a cCR. Defining who these patients are and how to best follow them is another critical need [20].

To improve the uniformity of response assessment, the Memorial Sloan Kettering three-tiered response/regression schema has been devised and is currently being tested prospectively [21]. This schema aims to provide quantitative endpoints for specific clinical, endoscopic and radiographic findings to allow for a precise and consistent evaluation of tumor response, with the goal of distinguishing patients with a cCR and thus candidates for WW, from those without a cCR and thus candidates for resection [21] (Table 11.1).

Table 11.1 Memorial Sloan Kettering regression schema [21]

	Complete response	Near complete response	Incomplete response
Images			
Endoscopy	Flat, white scar. Telangiectasia. No ulcer. No nodularity	Irregular mucosa. Small mucosal nodules or minor mucosal abnormality. Superficial ulceration. Mild persisting erythema	Visible tumor.
Digital rectal exam	Normal	Smooth induration or minor mucosal abnormalities	Palpable tumor nodules
MRI-T2W	Only dark T2 signal, no intermediate T2 signal AND No visible lymph nodes	Mostly dark T2 signal, some remaining intermediate signal AND/OR partial regression of lymph nodes	More intermediate than dark T2 signal, no T2 scar AND/OR No regression of lymph nodes
MRI-diffusion weighted	No visible tumor on B800-B1000 signal AND/OR Lack of or low signal on ADC map. Uniform linear signal in the wall above tumor is OK	Significant regression of signal on B800- B1000 AND/OR Minimal or low residual signal on ADC map	Insignificant regression of signal on B800-B1000 AND/OR Obvious low signal on ADC map

Clear definitions of both cCR and pCR are mandatory. Since pCR can only be objectively measured during pathologic evaluation after radical resection at present, it is considered the most reliable biological marker for local and distant tumor control and a predictor of improved oncological outcome [14, 22].

Methods for Assessing Clinical Response

Clinical Examination

In patients with locally advanced rectal cancer, the correlation between clinical response to NAT as assessed by digital rectal examination (DRE) and endoscopy, and pathologic response as measured after TME has been thoroughly investigated [23, 24].

In a single-institutional series, although 19% of patients had a cCR on examination, only 25% of these had a pCR. The sensitivity of cCR as a predictor of pCR was 77%, but the specificity was only 16% [23]. In another single surgeon study, DRE correctly detected only 21% of the patients with pCR [24].

Local Excision

Full thickness excision of tissue harboring residual cancer cells had been suggested as a way to evaluate the depth of invasion, and to serve as definitive treatment in some cases [25]. Unfortunately, pathological T stage does not correlate well with pathologic nodal status and the latter is not assessible by local excision. Furthermore, local excision after NAT can be associated with substantial rates of pain and wound dehiscence as reported in both retrospective series [26] and the prospective trial ACOSOG Z6041 [19]. Therefore, the authors feel that local excision in this context provides limited information about tumor response and recommend further research to determine its true clinical value.

Imaging

Magnetic Resonance Imaging (MRI) has been shown as a consistent tool to assess clinical response, given the ability of MRI to evaluate both regression and fibrosis on T2 weighted imaging. Based on these characteristics, the MERCURY Study group has developed an MRI Tumor Regression Grade System (mrTRG). This was shown to correlate with pathological T staging assessment and patients with mrTRG grades 1, 2 and 3 demonstrated significantly better survival than grades 4 and 5 [27]. Following this line of investigation, the TRIGGER Trial (NCT02704520) [28] which stratifies patients with mrTRG 1 and 2 to WW and mrTRG 3, 4 and 5 to further systemic chemotherapy, will provide insight and guidance concerning the utility of this classification system.

Metabolic imaging such as PET-CT has fallen short in this context to date. In a prospective diagnostic study, none of the individual PET parameters could identify pCR with a reliable degree of accuracy [29].

Clinical Considerations when Planning Watch and Wait

The risks for perioperative morbidity, as well as functional and quality of life sequelae of rectal cancer surgery have motivated the WW strategy. Currently, level I evidence for WW is lacking. Available data are from retrospective institutional series with highly variable selection criteria and treatment regimens and also from a prospective study that showed similar regrowth rates when a higher radiation dose was used [30]. In addition, the absence of uniform definitions for cCR, inconsistency in surveillance protocols and short-term study follow up, make the WW approach a treatment strategy that is still in the earliest stages of investigation. A recent synopsis of the current guidelines for WW summarized recommendations of 24 published guidelines around the world [31], with consensus that organ preservation for rectal cancer beyond low-risk T1 is still experimental and only indicated in patients who are unsuitable for radical surgery.

Local and Distant Failure

The major uncertainty regarding the WW strategy both in the context of a clinical trial and when completed off-protocol, is long-term oncologic results [14]. The fundamental difficulty lies in the correct identification of patients with favorable disease biology, who can be selected for WW and safely avoid radical resection (Fig. 11.1). The Habr-Gama group had reported local regrowth rates ranging from 2.8% to 30% depending on the series and on the length of follow-up [5, 16]

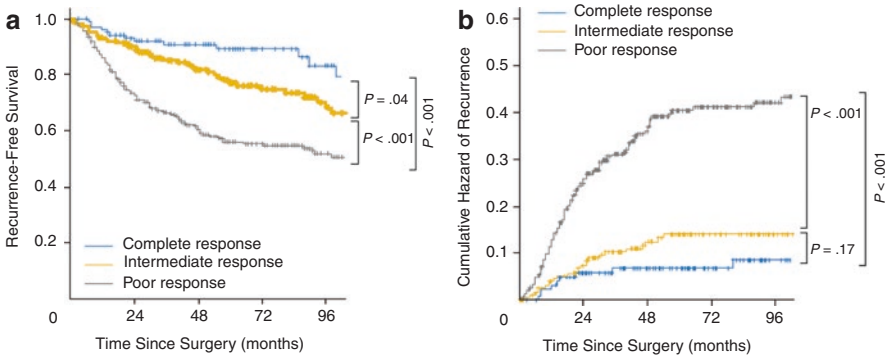


Fig. 11.1 (**a**) Recurrence free survival by response category. (**b**) Cumulative hazard of relapse by response category

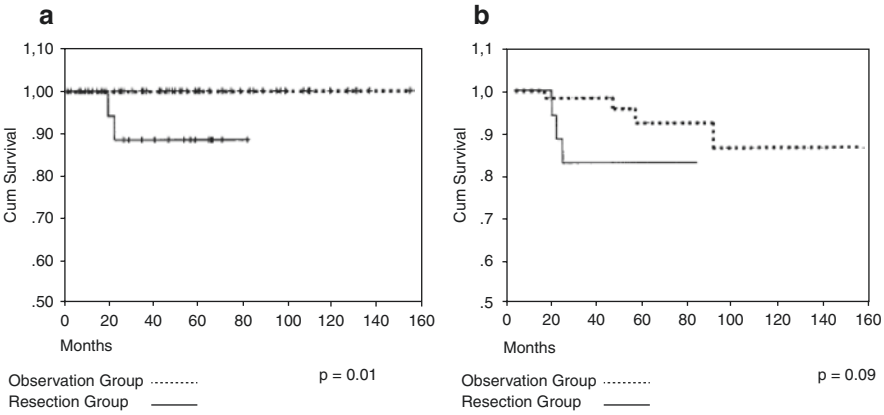


Fig. 11.2 (**a**), Overall survival. (**b**), Disease free survival

(Fig. 11.2). A recent systematic review showed a local regrowth rate of 21% and that surgical salvage was feasible in almost 93% of the cases [32]. Similar results were found in another systematic review of 867 pooled patients with a 15.7% two-year local regrowth, with 95.4% of these patients receiving salvage therapies [33] (Table 11.2). Nevertheless, both authors conclude that before this strategy can be widely implemented, further prospective data evaluated in the context of a clinical trial would be optimal.

A recent publication of the International Watch and Wait Database reported a 2-year cumulative incidence of local regrowth of 25.2%, among 880 patients who underwent WW after a cCR, and all regrowth cases were diagnosed within the first 2 years of surveillance. Distant metastasis was observed in 8% of the patients. The overall 5-year overall survival and disease-specific survival were 85% and 94%, respectively [41]. This is the largest study reporting pooled data related to WW post-NAT after achieving a cCR. It provides an estimation for the risks of local regrowth and of distant failure across multiple centers, in the context of an international database with the inherent limitations of selection bias, variable surveillance and heterogenous imaging details.

A concern that remains even in patients with apparent cCR, is that tumor regrowth can occur in the deeper invasive margin even if the mucosa appears normal [42]. A stricter surveillance protocol may be one way to address this issue but requires clear definitions, likely better endoscopic detection methods and pre-set triggers for further action; additionally, surveillance is likely to be effective only if these patients can be rescued with a secondary surgical procedure. Even when salvage surgery is feasible, it may be associated with a lower chance of sphincter-preservation [37]. Unpublished data from retrospective evaluation of a 10-year experience at Memorial hospital suggest a higher rate of distant metastases in patients with local regrowth when compared to those without local regrowth. Whether or not removing the primary tumor after completion of neoadjuvant therapy would have mitigated this risk is unknown (and impossible to ascertain given the small numbers), but this finding urges caution when selecting patients for a WW strategy.

Table 11.2 Outcomes of Watch and Wait versus surgical resection [33]

Watch and wait versus surgery with pathological complete response									
	N (% male)	**Median age (years; range)**	**Median follow-up (month)**	**Median distance from anal verge (cm; range)**	**Proportion of pCR (%)**	**Pretreatment TN stage (%T2, T3, N+)**	**2 year local regrowth (%)**	**2 year local recurrence (%)**	**Overall distant metastases (%)**
Araujo et al. [34]									
Watch and Wait	42 (40.5)	63.6 (NR)	48	≤5 cm = 83.8%	–	NR	9.5%	–	16.7%
Surgery	69 (49.3)	60.1 (NR)	47	≤5 cm = 59.4%	–	NR	–	2.9%	10.1%
Gossedge et al. [35]									
Watch and Wait	15 (NR)	75 (NR)	48	NR	–	NR, 67, 67	6.7%	–	6.7%
Surgery	13 (NR)	65 (NR)	61	NR	–	NR, 92, 100	–	7.7%	7.7%
Maas et al. [36]									
Watch and Wait	21 (67)	64.5 (49–79)	15	NR	–	24, 62, 71	4.8%	–	0
Surgery	20 (80)	66 (37–81)	35	NR	–	5, 85, 85	–	0	5.0%
Smith et al. [37]									
Watch and Wait	32 (NR)	70 (NR)	28	6 (0.5–12)	–	6, 89, 29	21%	–	8%
Surgery	57 (NR)	60 (NR)	42	7 (1–12)	–	13, 83, 40	–	0	2%
Smith et al. [21]									
Watch and Wait	18 (83)	62.3 (NR)	68	4.1 (NR)	–	6, 89, 39	5.6%	–	5.6%
Surgery	30 (67)	60.4 (NR)	46	6.0 (NR)	–	13, 83, 40	–	0	3.3%

Watch and wait versus surgery with clinical complete response									
	N (% male)	**Median age (years; range)**	**Median follow-up (month)**	**Median distance from anal verge (cm; range)**	**Proportion of pCR (%)**	**Pretreatment TN stage (%T2, T3, N+)**	**2 year local regrowth (%)**	**2 year local recurrence (%)**	**Overall distant metastases (%)**
Lai et al. [38]									
Watch and Wait	18 (83)	67.6 (NR)	50	3.35 (NR)	–	61, 39, NR	11.1%	–	0
Surgery	26 (46)	63.8 (NR)	42	4.81 (NR)	96.2%	31, 69, NR	–	0	3.9%
Li et al. [39]									
Watch and Wait	30 (60)	62 (NR)	58	3.5 (NR)	–	17, 50, 53	3.3%	–	3.3%
Surgery	92 (65)	56 (NR)	58	3.8 (NR)	88%	15, 52, 58	–	2.2%	6.5%
Seshadri et al. [40]									
Watch and Wait	23 (61)	50 (NR)	72	3.0 (0–6)	–	39, 61, NR	30.4%	–	13%
Surgery	10 (60)	55 (NR)	37	4.0 (0–7)	30%	40, 60, NR	–	0	20%

Functional Outcomes

The rates of bowel, sexual, and genitourinary dysfunction after NAT and WW remain unclear. Rectal preservation in the context of pelvic radiation (with associated rates of proctitis, nerve injury, and cystitis) may not mean that the patients are free from significant quality of life consequences. A case-matched study comparing 47 WW patients with 41 patients after NAT and TME, showed that QoL was better in several domains for the WW group [43]. Notably, a third of the WW patients experienced major low anterior resection syndrome (LARS) as measured by the LARS Score. In the authors' experience, WW patients usually report better bowel function when measured by the Memorial Sloan Kettering Cancer Center Bowel Function Instrument. However, prospective evaluation of these patient-reported outcomes is needed and is ongoing in the organ preservation in rectal adenocarcinoma (OPRA) trial.

Feasibility of Surveillance

Patients who are candidates for surgical resection of curative intent who choose to undergo WW require intensive surveillance. This typically includes frequent clinical, laboratory, endoscopic, and radiographic examinations. Such a surveillance program is resource-intensive, and requires an established infrastructure within the healthcare system. Whether it is cost-effective compared with standard of care measures in the long-term is unknown. It can also be a burden on the patients both practically and psychologically. Finally, appropriate expertise in multiple disciplines is necessary to enable the treatment team to accurately assess disease status and to triage the patient for continued WW vs. salvage treatment or intervention.

Future Strategies for Refining Watch and Wait

Improving Tumor Response to NAT

Improving rates of excellent response to NAT is likely to improve overall outcome of patients who undergo WW. Several strategies can be utilized alone or in combination, and have included enhanced chemotherapy strategies, novel radio-sensitizing agents, modulation of preoperative radiation therapy dosing (e.g. dose escalation), and increasing the "wait" period.

Current evidence suggests that the grade of response is correlated with the dose of radiotherapy. Therefore, dose escalation strategies have utilized various techniques such as external beam radiotherapy, brachytherapy, contact radiotherapy and proton/iron beam radiotherapy. In a comparative effectiveness database study, a

pooled analysis of nearly 3300 patients showed that the dose of neoadjuvant radiation was a significant predictor of pCR in a multivariate analysis that included also clinical T stage and the time interval between the completion of neoadjuvant CRT and surgery [44]. However, neoadjuvant brachytherapy boost did not afford significant additional benefit in survival or local recurrence when given after standard NAT and TME [45]. In summary, in spite of these retrospective analyses showing a higher rates of pCR it is unknown whether a dose escalation approach will lead to a higher rate of organ preservation in the context of a prospective trial.

The use of systemic chemotherapy to improve pathologic response to NAT has been proposed based on evidence that systemic chemotherapy can lead to pCR alone [46]. The CAO/ARO/AIO-04 German randomized phase III trial showed higher rates of pCR in locally advanced rectal cancer patients when oxaliplatin was added to fluorouracil-based NAT [47]. Although these results were encouraging, other reports assessing the addition of oxaliplatin to chemotherapy regimens for rectal cancer patients demonstrated a considerable increase in toxicity with no improvement in the rates of pCR [48]. However, additional duration of multi-drug systemic chemotherapy either before or after standard NAT is currently being tested in several clinical trials.

Finally, it is well recognized that a longer interval between NAT and surgery is associated with higher rates of pCR. Using the concept of extended observation, the introduction of chemotherapy during the "wait" period has shown promising results. The Timing of Rectal Cancer Response to Chemoradiation Consortium trial showed a 38% rate of pCR if 6 cycles of FOLFOX were given in an extended "watching" period compared with the 18% in the chemoradiation alone group [49]. Currently an ongoing prospective study (NCT01558921) is evaluating the survival outcomes associated with short-course radiation followed by capecitabine/5FU and oxaliplatin chemotherapy and surgery [50]. Finally, the results of the ongoing OPRA Trial [21], Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management, are expected to provide more information about the role of total neoadjuvant chemotherapy in combination with chemoradiation in WW strategies.

Conversion of Near-Complete to Complete Clinical Response

A subset of patients achieve a near-complete CR to NAT and are potential candidates for WW if the response evolves to a cCR with more 'waiting', thus avoiding TME. Data from a prospective cohort study showed that 62% of the patients that had a near-complete CR after CRT did achieved a cCR after waiting an additional 3 months after the initial assessment [51]. Currently, there is no consensus or prospective protocol for standard management of these patients. Firstly, the status of a near CR must be defined as precisely as possible using DRE, endoscopy and

MRI. Next, consolidation chemotherapy in the context of total neoadjuvant therapy may be considered in an attempt to enhance response (off protocol). These highly selected patients must be counseled carefully and must understand that the proposed treatment strategy is still experimental and that they may require more frequent monitoring. They must also understand that a part of the fiduciary contract includes strict compliance with active surveillance and their willingness to undergo surgical resection if local regrowth ensues. Finally, they should be counseled that neither the feasibility of salvage surgery nor the ability to preserve the sphincter can be guaranteed and will depend on assessment at the time of tumor regrowth. Meticulous documentation and a carefully prescribed, patient-specific follow-up regimen/surveillance strategy is essential. It should be noted that the OPRA trial does allow for consideration and additional time for evolution of response to cCR in these near-complete CR patients.

Response Prediction Tools

In the search for better ways of assessing the response to NAT, novel tools have been tested. Dynamic contrast-enhanced (DCE) MRI may provide improved diagnostic potential following NAT. This technique evaluates the vascularity of a tumor, providing valuable information about the biological aggressiveness and the degree of neovascularization, and can thus aid in the assessment of tumor response to NAT. A recent systematic review showed that DCE-MRI can identify tumors that exhibit a high pre-NAT K_{trans} (representing the rate at which the contrast agent transfers from the blood to the interstitium) along with a subsequent decrease in K_{trans}. These both appear to be significant predictors of a favorable response to NAT [52]. On the other hand, a 5-point MRI tumor regression grade (mrTRG) based on the amount of tumor fibrosis has been developed and is currently being prospectively tested in the TRIGGER trial.

Radiomics represents another promising tool. It utilizes advanced imaging pattern recognition tools to extract quantitative characteristics from a large quantity of digital data to determine the relationships between the image data and the underlying pathophysiology [53]. A recent report constructed a radiomics signature using 2252 features from each patient based on imaging pre- and post-NAT. This signature showed good discrimination of pCR when used in combination with tumor length (AUC 0.9756 95% CI, 0.9185–0.97) [54]. Notably, there is emerging evidence that radiomics data T2-weighted–MRI images could classify pCR better than qualitative assessment and diffusion-weighted imaging [55].

Finally, molecular markers that can individually predict the risk of disease relapse may significantly aid in the identification and selection of patients who are safe candidates for WW. For example, a recent publication suggested that *Akt* activation could play an important role in the response to NAT, and prior work from Garcia-Aguilar et al. implicated double mutant *TP53/KRAS* patients as refractory to NAT (with validation), but no prospectively validated molecular predictor has been

established to date [56]. Clearly there is a need for the identification and validation of other predictive biomarkers, and will likely require both pooled analysis of clinically annotated retrospective data as well as prospective evidence.

Conclusion

Watch and wait is a promising treatment strategy in selected patients who achieve cCR after NAT although its long-term oncologic safety remains to be established. The future success of WW will require additional research toward maximizing tumor response to NAT, improving the prediction of response, standardized assessment of cCR, optimizing surveillance, and evaluating the multi-dimensional impact of WW. Prospective controlled clinical trials are essential to inform the safety and efficacy of a WW approach. Until then, WW may be offered to patients with contraindications to radical surgery and to those willing to take on the potential oncologic risk off-protocol, but ideally should be conducted in the setting of a clinical trial.

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Chapter 12
The Watch and Wait Approach After Neoadjuvant Therapy: The Australian Viewpoint

Joseph C. Kong and Alexander G. Heriot

Introduction

The current standard of care for locally advanced rectal cancer (T3-4 and/or N+) is neoadjuvant chemoradiotherapy (CRT) before total mesorectal excision (TME). This approach is taken due to the anatomical location in the narrow confines of the pelvis. By appreciating the anatomical restriction within the pelvis, the risk associated with surgery without neoadjuvant chemoradiotherapy (CRT) is a positive circumferential resection margin (CRM). This is associated with higher rates of local recurrence [1]. Historically local recurrence rates were as high as 40%, and perhaps the most prominent study showed a rate of 27% in the control arm of the Swedish rectal cancer trial conducted in 1997 for immediate surgery when compared with 11% in the short-course CRT arm [2]. Subsequently, further trials comparing neoadjuvant CRT with immediate surgery showed improvements in local disease control. Other benefits of neoadjuvant CRT include an increase in the radiation effect (as local blood supply is not damaged and tumour oxygenation is paramount for radiation sensitivity), minimising radiation toxicity, and most importantly, potential down-staging of the tumour [1–3].

Following concerns with high pelvic failure and the local recurrence rate, in 1988 Bill Heald described the ideal resection plane, also known as the "holy plane" of surgical rectal dissection [4]. Today it is the standard operative technique, and is

J. C. Kong
Department of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

A. G. Heriot (✉)
Department of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

University of Melbourne, Melbourne, VIC, Australia
e-mail: alexander.heriot@petermac.org

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best known as TME, which requires the operator to perform a meticulous dissection in the extra-fascial plane. This maintains an intact fascia envelope of the posterior, lateral and distal mesorectum as these locations harbour lymph nodes, which are the basis of a danger zone around the visible and palpable tumour. Through this innovative technique and neoadjuvant CRT, the current local recurrence rate is now quoted as 5–7% [5, 6].

The Evolution of "Watch and Wait"

The next development was a keen observation that there is a spectrum of tumour responsiveness following neoadjuvant CRT. An estimated 10–25% of locally advanced rectal cancer treated with CRT will achieve a pathological complete response (pCR), defined as no residual tumour identified by a pathologist in the resected specimen [7–9]. In addition there is the survival benefit in achieving a pCR, with a pooled local recurrence rate of 0.7%, a distant recurrence rate of 8.7%, a 5-year overall survival of 90.2% and a disease-free survival of 87% [10]. Recognising this clinical entity resulted in the recognition of a new concept that contrasted with the traditional orthodox teaching [11]. This concept involved a non-operative approach similar to the management of anal squamous carcinoma following CRT [12].

The rationale for pursuing this "watch and wait" strategy was the potential for avoiding the sequelae of radical surgery, which included long-term urinary dysfunction, sexual dysfunction and faecal incontinence. There are also immediate postoperative risks to consider such as bleeding, infection and anastomotic leak [13]. From the patient's perspective, most would also prefer to avoid the need for a temporary or even a permanent stoma, maintaining gut function and their quality of life [14]. For these reasons, there have been increasing trials assessing the safety of the "watch and wait" strategy [15–18].

The first published series of patients was by Nakagawa et al. in 2002. Ten patients who were deemed to have clinical complete response (cCR) went on to have active surveillance [11]. However, 8 patients subsequently developed local tumour regrowth within 8.8 months and the authors concluded that the "watch and wait" strategy was not a safe option. Subsequently in 2004, Habr-Gama et al. from Sao Paulo, Brazil continued research on the "watch and wait" strategy by publishing their series of 71 patients with cCR, reporting robust long-term outcomes [19]. Despite this, for a period of time they were the only advocates of the "watch and wait" strategy and in their most recent publication of 90 patients diagnosed with cCR, 28 patients (31%) had tumour regrowth with an overall salvage rate of 93% (26 patients) [18]. They then reported a 5-year cancer-specific overall survival (OS) and disease-free survival (DFS) of 91% and 68%, respectively. This led to a progressive acceptance and gradual increase in the number of trials conducted assessing the safety of this strategy [20–25].

Trials and Long-Term Outcomes

There have been numerous systematic reviews and meta-analyses summarising the available publications on a number of clinical end-points concerning the safety of a "watch and wait" strategy [26–29]. One of the main concerns is that there is no reliable test that can accurately stratify patients to pCR [30]. As a result, cCR was devised as a surrogate assessment for pCR. This would mean that although patients can avoid the morbidity associated with surgery, they still have a risk of tumour regrowth and consequently will need intensive surveillance.

All studies identified were case-controlled cohort studies (level II evidence) [26, 27], with only one propensity-matched multicentre trial identified from the Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) group [25]. There was significant heterogeneity between all the studies, with no randomised controlled trials to date. In a pooled analysis by Kong et al. comparing "watch and wait" approach to TME after neoadjuvant CRT, the local tumour regrowth rate was 28.4%, distant recurrence was 1.9% and salvage surgery for tumour regrowth was possible in 83.8% of patients [26]. As for the long-term survival, no pooled analysis was performed due to reporting heterogeneity. Nonetheless in a well-constructed, propensity-score matched cohort analysis by the OnCoRe group there was reported no difference in 3-year non-regrowth DFS between "watch and wait" (88% [95% CI 75–94]) and TME (78% [63–87]). Similarly, no difference was noted in 3-year OS with the "watch and wait" approach – 96% (88–98%) when compared with a TME – 87% (77–93%).

Other authors have identified similar survival outcomes, including Maas et al. and Smith et al. who demonstrated no significant differences in 2-year OS; 100% and 97% ("watch and wait") vs 91% and 100% (TME) and 2-year DFS; 89% and 88% ("watch and wait") vs 93 and 98% (TME), respectively [22, 31]. Despite equivalent survival outcomes to date, these were small observational cohort studies with a short follow-up and should be interpreted with caution.

Patient Selection and Assessment of Clinical Complete Response

A stringent selection process is required for "watch and wait". The initial selection includes all patients with histological confirmation of rectal adenocarcinoma, radiological staging of T2-4 and/or nodal positivity confined to the radiation field and patients who will receive long course chemoradiotherapy can be considered [25, 27, 32]. The long course neoadjuvant treatment usually consists of radiotherapy (45–65 Gy), for which 50.4 Gy was the most common dose, with concurrent fluoropyrimidine-based chemotherapy [26].

Table 12.1 Assessment of clinical complete response in each study published to date

Method of assessment	Criteria for complete clinical response
Digital rectal examination	Absence of a palpable tumour [22, 25, 34]
Endoscopic visualisation (Use Maas et al. [34] assessment)	No residual tumour [22, 31] OR whitening of mucosa with telangiectasia [16] OR small ulcer with smooth edges [34]
Biopsy	Negative if there was a scar or ulcer identified [21, 22, 31]
Magnetic Resonance Imaging [27, 34]	Normal rectal wall/no residual tumour OR only subtle wall thickening OR residual fibrosis AND no involved lymph node

A consideration is the timing of assessment of the irradiated tumour bed. In this regard, it has been shown that a longer interval time between cessation of CRT to the time of surgery increases down-staging and the pCR rate [33]. Hence, in the observed studies, the interval time to assessment for selecting cCR varies between 6 and 12 weeks [19, 23–25]. Furthermore, there is currently no standardised definition for cCR and surgeons currently rely upon institution-specific definitions. A multimodality approach is used to assess these patients, and will usually include digital rectal examination (DRE), endoscopic visualisation of the previously irradiated tumour bed and magnetic resonance imaging (MRI). The commonly accepted findings for cCR for each modality are shown in Table 12.1.

Increasing Pathological Complete Response Using Different Neoadjuvant Regimens

There have been a few attempts to deliver intensified regimens to improve the rate of pCR. These include increasing the dose of radiotherapy [23] and adding a new combination of chemotherapeutic agents [35, 36]. As such, Appelt et al. had used 60 Gy to the local tumour site and 50 Gy to the lymph node basins in 30 fractions, with an additional 5 Gy boost to the endorectal region and tegafur-uracil as their preferred chemotherapeutic agent [23]. They reported a persistent cCR rate of 62% (31 out of 50 patients) and a tumour regrowth rate of 22.5% (9 out of 40 patients) after a median follow-up of 34.5 months [23]. However, in a meta-analysis assessing an intensified radiotherapy dose of ≥60 Gy from 14 studies with a total of 487 patients, they found no correlation with pCR rate [37].

Others have reported an addition of another chemotherapeutic agent such as oxaliplatin [36], anti-epidermal growth factor and anti-vascular endothelial growth factor to the current standard treatment [38, 39]. Although showing promising results initially, larger studies concluded that these therapies do not increase the tumour response rate for locally advanced rectal cancer.

Intensive Surveillance During "Watch and Wait"

Following the selection of patients with cCR, they will then need to continue an intensive surveillance protocol in order to ensure that no local tumour regrowth has occurred. The surveillance protocol commonly consists of clinical assessment by DRE, proctoscopy or endoscopy, serum carcinoembryonic antigen (CEA) measurement and imaging modalities such as MRI to detect local/regional tumour regrowth and positron emission tomography/computed tomography (PET/CT) for the detection of distant recurrence. An example of a PET/CT response to chemoradiation is seen in Fig. 12.1.

However, there is no agreed consensus on the frequency and timing for each modality. The protocol established by Habr-Gama et al. since 2004 were DRE and CEA measurement every 2 months in the first year, every 3 months in the second year and then 6 monthly in the third year and beyond. This was followed by radiological assessment using MRI and CT of the abdomen and pelvis every 6 months for the first 2 years, followed by yearly thereafter [32]. In comparison, the OnCoRe group evaluates DRE and MRI to every 4–6 months in the first 2 years and uses other forms of assessment per their standard national guidelines; including a colonoscopy at 1 year, CEA every 6 months for 3 years and CT of the abdomen and chest with a minimum of two scans in 3 years [25].

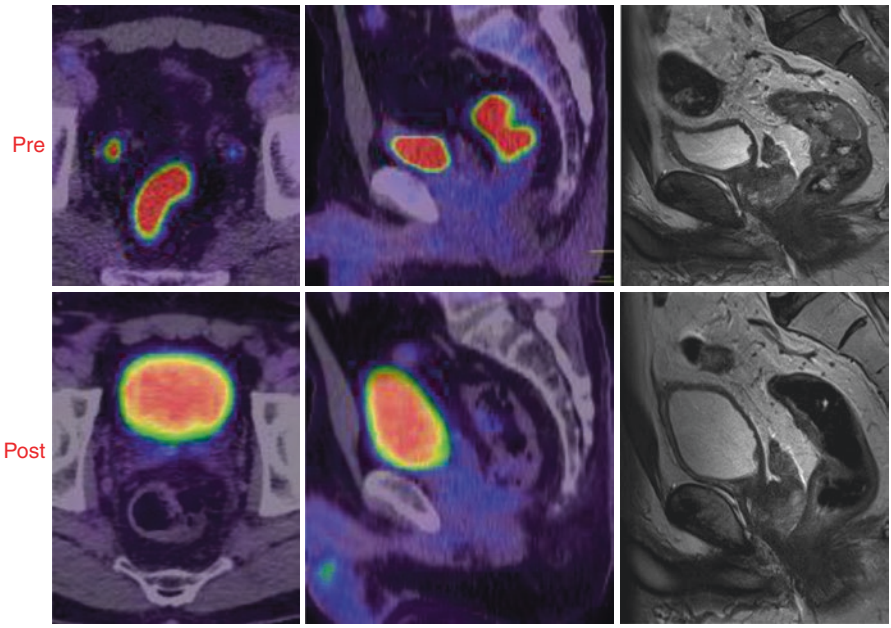

Fig. 12.1 Complete pathological response of rectal cancer on imaging (PET and MRI) pre and post neoadjuvant chemoradiotherapy

Without an agreed standardised protocol, a systematic review from Sammour et al. made recommendations from the summation of all published protocols. These include DRE, endoscopy and CEA every 3 months for the first 2 years and every 6 months thereafter, with biopsies undertaken for any suspicious lesions. Patients are also recommended for an MRI every 6 months for the first year, and a CT of the abdomen and chest every 6 months for the first year, and annually thereafter up to 5 years.

Patterns of Local Failure

Local tumour regrowth is a term used for incomplete sterilisation of rectal adenocarcinoma on a previously irradiated tumour bed after failure with the "watch and wait" strategy. Surveillance for "watch and wait" has shown a tumour regrowth rate between 6% and 34% [25, 31, 32, 40]. In a large retrospective database collated by the International Watch and Wait Database (IWWD) which presented their series of 679 patients with cCR, there was a local tumour regrowth rate of 25% over a median follow-up of 2.6 years (0–24 years) [41]. Of their series of local tumor regrowth, 96% were endoluminal tumours whereas 4% were lymph node metastases. These were all early detections, with 84% identified within the first 12 months. This was consistent with the reported outcomes by the most experienced group led by Angelita Habr-Gama which showed that all of their cases of local tumour regrowth occurred within the first 24 months, after a median follow-up of 60 months. Hence, an intensive surveillance program was developed for early identification of local tumour regrowth with the potential for salvage surgery.

Role of Adjuvant Chemotherapy

The basis for recommending adjuvant chemotherapy came before surgical refinement to the currently known TME. Patients with stage II and III rectal cancers will typically be offered 5-fluorouracil or capecitabine and oxaliplatin [42, 43]. Subsequently a randomised controlled trial by the European Organisation for Research and Treatment of Cancer (EORTC) 22921 (Radiation Therapy, Surgery and Chemotherapy in Treating Patients with Rectal Cancer that can be Surgically Removed) [44], concluded that adjuvant fluorouracil-based chemotherapy after neoadjuvant CRT does not affect DFS or OS.

It is in that context, that the uptake of adjuvant chemotherapy in the "watch and wait" trials has been variable. There have been three studies that had included adjuvant therapy as part of their trial protocol whereas only one study was an off-protocol administration [26]. The question remains as to whether cCR patients with nodal involvement on pre-treatment imaging require additional therapy, especially with the knowledge that not all lymph node positivity will be detected by such imaging [45].

Limitations in Predicting Pathological Complete Response

One of the fundamental concerns with the "watch and wait" strategy is the risk of tumour regrowth and the ability to perform salvage surgery. As cCR is not equivalent to the gold standard histological assessment of pCR, others have searched for a better test. Identifying the extent of tumour response can be categorised as (1) clinical assessment, (2) imaging, (3) laboratory testing, (4) genomics and (5) immune profiling.

Clinical Assessment

Digital rectal examination, endoscopy and biopsy play an essential role in the assessment of cCR [26]. DRE allows assessment of tumour size, morphology, mobility, and circumference. The limitation is the discordance between the surgeon's assessment and the pathological response, as demonstrated by Guillem et al. [46]. In a single surgeon clinical assessment, before and after neoadjuvant CRT, the study found only 21% pCR were identified correctly [46]. The reasons for the poor correlation with DRE include: those cases where the tumours are beyond the reach of the examiner's finger, where there is difficulty in distinguishing between fibrosis and microscopic tumour in the bed on palpation and where there is a subjective interpretation of tumour response.

As for endoscopic visualisation and biopsy, it had similar accuracy to DRE, with only 59% diagnosed correctly in one prospective study [47]. Poor detection rates can be explained by a single study investigating the distribution of residual rectal cancer after neoadjuvant CRT within different layers of the bowel wall [48]. A total of 79 patients were recruited, and the distribution of residual rectal cancer for ypT2-4 (where yp denotes staging after neoadjuvant CRT) in the mucosa, submucosa, and muscularis propria was 20%, 36.7%, 69.2%, respectively. This resulted in an overall sensitivity of 12.9% and a specificity of 94.1%. The study concluded that the rectal cancer residuum was primarily located in the deeper layers of the bowel wall, and that the biopsy results for primary rectal lesions were unreliable [48]. Moreover neither DRE nor endoscopy can assess nodal involvement after neoadjuvant CRT. An example of an endoscopic response is seen in Fig. 12.2.

Imaging

Restaging after neoadjuvant CRT in locally advanced rectal cancer is not routine practice. Imaging modalities can include endorectal ultrasound (ERUS), MRI and PET/CT.

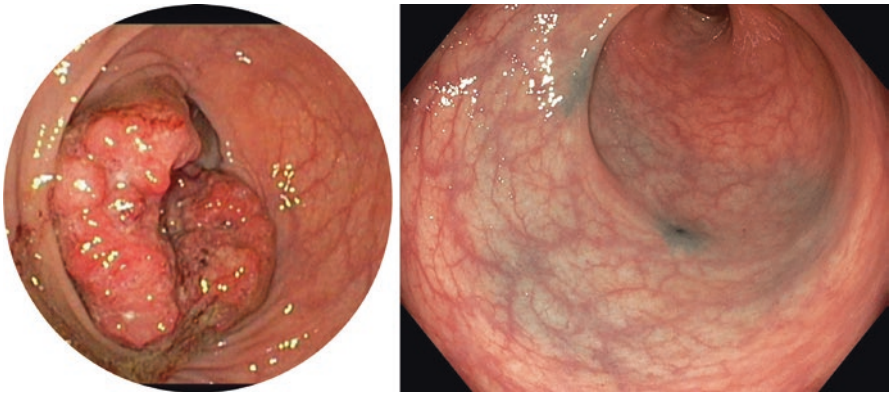

Fig. 12.2 Endoscopic view of rectal cancer before and after neoadjuvant chemoradiotherapy after complete clinical response

Endorectal Ultrasound

Assessment by ERUS has been shown not to be accurate, owing to the inflammation, necrosis and desmoplastic changes identified after neoadjuvant CRT. The overall ypT stage accuracy was highly variable, between 43% and 73%. However ERUS may have a role in confirming lymph node negativity after pre-operative treatment, with a ypN stage accuracy of 72–77% in those with pCR [49–53]. In one study, six of six patients were correctly diagnosed with absence of lymph node involvement [52] and in three studies, the negative predictive values were between 81% and 88% [47, 52, 54].

Magnetic Resonance Imaging

Pre-operative MRI has been the key imaging modality to assess T and N stage as a guide to clinical management. In the last 6 years, two emerging groups (Regina Beets-tan et al. and Gina Brown et al.) have investigated the utility of re-staging MRI to assess pCR. Similar to DRE, the limitations of MRI are the inability to differentiate residual tumour from fibrosis, desmoplastic reaction, inflammation and oedema surrounding the tumour bed post-therapy [34, 55]. An extensive systematic review performed by Ryan et al. showed the accuracy of standard MRI in assessing T and N stage were 45–67% and 65–75% respectively. [30]

Championing the usage of restaging MRI is the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) group, whose focus was to assess the accuracy of MRI in determining multiple facets of tumour response after neoadjuvant CRT in relation to short-term (tumour regression) and long-term DFS

Table 12.2 The criteria for the assessment of mrTRG

mrTRG	Definitions
1	No/minimal fibrosis visible (tiny linear scar and no tumour signal)
2	Dense fibrotic scar (low signal density) but no macroscopic tumour signal (indicates no or microscopic tumour)
3	Fibrosis predominates but obvious measurable areas of tumour signal visible
4	Tumour signal predominates with little/minimal fibrosis
5	Tumour signal only (no fibrosis, includes progression of tumour)

and OS [55–57]. In the process, the authors have developed the MRI tumour regression grade (mrTRG), to stratify good and poor responders [55]. In addition, they discovered extra-mural venous invasion (EMVI) was significantly predictive of poor responders in their updated series, when added to the mrTRG (Table 12.2) [58]. In their multivariate Cox-regression analysis, mr-vTRG 4–5 increased the risk of disease recurrence with an estimated HR of 5.75, and they concluded that it can be used to identify high risk patients for more intensive therapy. Because patients were stratified as good versus poor responders, the accuracy to predict pCR using re-staging MRI is uncertain.

In a large (1566 patients from 33 studies) meta-analysis performed by van der Paardt assessing the accuracy of re-staging MRI in predicting pCR, they found a re-staging MRI sensitivity and specificity of 19% and 94%, respectively. This result was enhanced by applying diffusion weighted imaging (DWI), with a significant increase in sensitivity to 84% but with a lower specificity of 85% [59]. Because of the heterogeneous results with re-staging MRI accuracy, this modality cannot be relied upon to dictate a non-surgical rectal conserving approach.

Positron Emission Tomography/Computed Tomography

PET/CT is a nuclear medicine imaging technique that acquires a 3-D image of the body. A small amount of radioactive fluorodeoxyglucose (FDG) tracer is injected through a vein, and will be taken up by all active tissue. But, because cancer cells grow rapidly, there is an increased uptake at the cancer site when compared with normal healthy tissue. Hence, the degree of metabolic response (measured by FDG uptake), before and after neoadjuvant CRT, correlates with the tumour regression grade allowing differentiation of responding from non-responding tumours with an overall accuracy of 80% [60]. Other authors have reported similar accuracy rates for different standardized uptake value (SUV) mean reductions. Cascini et al. found that a threshold of 52% decrease in the SUVmean resulted in an accuracy of 100% when distinguishing histologic responders from non-responders. When using SUVmax values, a cut-off of 42% decrease in the SUV max identified responders from non-responders with an overall accuracy of 94% [61].

There are still reservations about relying upon PET/CT as a predictor of pCR, due to the limited number of studies and the fact that there is as yet no set standardized assessment of tumour response or a designated cut-off mean value in the reduction of metabolic activity. Furthermore, false positive tests have been reported due to inflammatory changes without any residual disease being found in the tumour bed [62].

Combining Clinical Assessment with Imaging Modalities

A potential method to improve the accuracy of predicting pCR is to combine clinical assessment (digital rectal examination, endoscopy for mucosal assessment and biopsy of suspicious lesions) with imaging. The addition of radiological assessment has shown encouraging results in increasing the detection of pCR [34, 63–65]. Two of the most promising modalities in combination with clinical assessment are (PET/CT) [65] and magnetic resonance imaging with diffusion weighted imaging (MRI DWI) [34].

Habr-Gama's group from Sao Paulo investigated the utility of PET/CT in predicting cCR, reporting an accuracy approaching 91% [65]. When clinical assessment was combined with PET/CT, the accuracy increased to 96%. The high fidelity in these results is likely due in part to the vast experience accrued over the last two decades by this pioneering group as evidenced by their serially published updates [19, 32]. In the same manner, Maas et al. reported a clinical assessment sensitivity and specificity of 53% and 97%, respectively, which when combined with MRI DWI led to a post-test probability of predicting cCR of 98% [34]. Both MRI and PET have shown great promise when combined with clinical assessment as part of a multi-modal technique in evaluating the tumour response rate after neoadjuvant CRT. What is currently lacking is a randomised, single-blinded trial of PET/CT or MRI, although the current TRIGGER trial, a multicentre randomised controlled trial assessing the utility of the magnetic resonance tumour regression grade (mrTRG) as a novel biomarker designed to stratify patients between good and poor responders to chemotherapy, may provide some answers to this question.

Laboratory Testing

Two distinct markers have been consistently associated with pCR; namely, the carcinoembryonic antigen (CEA) level [66, 67] and the neutrophil-lymphocyte ratio (NLR) [68, 69]. Both are routinely performed as part of the patient's clinical work-up for rectal cancer management. However, discrepancy in the mean cut-off point or reduction value makes it difficult to ascertain the true value and significance of these markers. A study by Perez et al., with 170 patients who received neoadjuvant CRT

followed by surgery, found that a post-treatment CEA level of <5 ng/ml was associated with increased rates of pCR [66] whereas in another study by Wallin et al. recruiting 530 patients treated with preoperative CRT and radical surgery, 96 patients had pCR, with pre-treatment CEA levels of 3.4 versus 9.6 ng/ml being strongly associated with pCR [70]. Similar results can be extrapolated from NLR [68, 69], and it is likely there is a range of cut-off points that need to be established through a much larger, multicentre study so as to ensure clinical applicability.

Genomics

It is thought that a panel of genes will be able to stratify patients into high or low risk categories, providing an objective test which informs patient risk and which justifies the use of adjuvant chemotherapy. The first commercially available gene expression panel was the Oncotype Dx colon cancer test, a multi-gene test for predicting the risk of recurrence in patients with stage II and III colon cancer [71]. Other gene expression panels are also available such as ColoPrint and ColDx, both reported to be robust diagnostic platforms in refining the prognosis of Stage II and III colon cancer [72, 73]. Although promising in colon cancer cohorts, currently there are no data on the relevance of these commercially available gene expression panels in rectal cancer after neoadjuvant CRT.

Nonetheless, a wide variety of genetic and molecular markers have been implicated in the prediction of response to neoadjuvant CRT, and some of these were highlighted in a comprehensive systematic review by Spolverato et al. [74]. In the review, the authors showed that epithelial growth factor receptor (EGFR), thymidylate synthase genes, bcl-2/bax and cyclooxygenase-2 were promising biomarkers in predicting the response to neoadjuvant CRT, but the value of p53, Ki-67 and p21 testing remains controversial. Hence, no specific biomarker(s) have yet been conclusively proven to be robust for clinical utility and a better predictive tool is still required.

Immune Profile

The immune system is a host defence mechanism capable of protecting against a number of threats including cancer. In a seminal paper by Galon et al. cytotoxic tumour infiltrating lymphocytes (TILs), were described as key arbiters of a good prognosis [75], and subsequently a similar correlation was demonstrated with the image analysis densities of CD8 + cytotoxic TILs detected in the pre-treatment biopsies of the good pathological response patients who had received long-course CRT for their locally advanced rectal cancer [76]. These findings have led to a number of studies assessing the predictive value of cytotoxic TILs [77–79], however there are several limitations with these studies. Firstly, the cut-off values for

stratifying patients to either high- and low-density TILs were different between studies with each requiring a pre-determination for new institutions; a finding which Galon et al. have demonstrated during the initial creation of their in-house Immunoscore [75]. Secondly, the dichotomization of outcomes, (between a good and a poor response), does not specifically answer the question of the accuracy for predicting response to therapy in individual patients. Thirdly, there is the observation that a subset of patients with a high TIL density can have a poor response. Consequently, at the present moment the assessment of the density and type of TILs derived from pre-treatment biopsies is not the standard of care and more studies are required in order to assess the feasibility and accuracy of predicting pCR.

Should Patients "Watch and Wait"?

As research to identify a robust investigation continues, clinicians will need to weigh the risk and benefits of the "watch and wait" strategy with the individual patient. The avoidance of radical surgery (and a stoma) needs to be weighed against local tumour regrowth risk and the need for intensive follow-up for at least 2 years. There are still uncertainties with longer survival outcomes with both rectal preservation and salvage surgery, especially with respect to functional impact. Therefore the "watch and wait" strategy should be recommended with caution, and in a multidisciplinary team environment with the ability to deal with surveillance, decision making for adjuvant chemotherapy and local tumour regrowth. Those patients who are high surgical risk and with a shorter life expectancy, such as the elderly or those requiring an abdominoperineal resection can be considered after appropriate informed consent.

Given the uncertainty of long-term outcomes, meticulous prospective data collection must be enforced with continuous audits to ensure a high quality of assessment and care delivered to patients during a "watch and wait" strategy. An alternative is a formal collaboration with the International Watch and Wait Database group so as to facilitate and refine practices associated with the rectal preservation approach.

Future Direction

The research focus into novel therapies has now shifted towards harnessing the patient's immune response so as to increase the pCR rate. Collectively these treatments, the immunotherapies are being assessed with a number of Phase I/II clinical trials underway in the neoadjuvant setting. These include the ExIST study of Galunisertib (a transforming growth factor-beta kinase inhibitor; clinical trial identifier NCT02688712) and the R-IMMUNE study of atezolizumab (an anti-programmed cell death-ligand 1; clinical trial identifier NCT03127007).

Furthermore, data from the TRIGGER trial (clinical trial identifier: NCT02704520) designed to assess the utility of mrTRG in stratifying patients for the management of rectal cancer patients, are eagerly awaited.

Summary

The "watch and wait" strategy is currently not the standard of care for locally advanced rectal cancer. This is due to an inability to predict pCR accurately compounded by uncertainty in the long-term survival and functional outcomes. There is a small subset of patients which might prove appropriate for such a strategy, however, the data from these ongoing trials are awaited.

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Chapter 13
Intersphincteric Resection: Indications and Outcome

F. D. McDermott, N. J. Smart, and D. C. Winter

Introduction

Despite advances in the management of rectal cancer, surgery remains the mainstay of treatment with curative intent. The major advance in rectal cancer care was the standardization of surgical technique, total mesorectal excision, along with pathological reporting of the excised specimen that led to reductions in local recurrence and improved survival [1–3]. Abdominoperineal excision of the rectum (APR) was once the only option for low tumors but sphincter-preserving surgery is now commonly performed. Despite these options there exists a wide variability in the proportion of patients with rectal tumors that undergo APR (12–51%) [4–6]. The improvements in neoadjuvant therapy have led to better down staging of tumors and in some cases pathological complete response (pCR) [7]. This allows previously inoperable tumors to undergo surgical management or perform less invasive procedures such as local excision or sphincter-preserving surgery.

Reducing APR rates has been made possible by challenging doctrine, such as the 5 cm cut-off that previously precluded any tumor in the lower rectum being treated with anything other than APR [8], neoadjuvant chemoradiotherapy, and advancements in surgical technology [9–11]. The 5 cm rule was challenged by a pathology study that found that there was less than 1 cm distal intramural spread of tumors [8]. Ultra low rectal cancers present a surgical challenge to achieve the widely agreed 1 cm oncological clearance whilst preserving the continuity of the gastrointestinal tract [12]. ISR is one technique that has been used to manage these low rectal tumors less than 1 cm from the dentate line without detriment to oncological outcomes [13].

F. D. McDermott · N. J. Smart
Royal Devon & Exeter Hospital, Exeter, UK

D. C. Winter (✉)
Department of Surgery, St Vincent's University Hospital, Dublin, Republic of Ireland

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What Do We Mean by Intersphincteric Resection?

Sphincter preserving surgery is not a recent invention but ISR was first coined as a term in the 1990s with a series of 38 patients demonstrating a reasonable local recurrence rate of 11% (for the period) [14]. It is a procedure aimed at tumors of the lower rectum that can usually be assessed digitally as they are within 4–8 cm from the anus. Indications include carcinomas, villous adenomas, carcinoids and hemangiomas. Contraindications are undifferentiated cancers, T4 tumors and those that have invaded the sphincter apparatus [13]. Relative contraindications are those with poor sphincter function. Intersphincteric resection is a two-stage procedure comprising a perineal dissection in the intersphincteric plane and an abdominal component with total mesorectal excision (TME) to meet the dissection from below [1]. The internal sphincter is removed with the specimen leaving the external sphincter to aid in post-operative continence function. The final stage is a hand-sewn colo-anal anastomosis. The abdominal component can be performed open, laparoscopically [15], via single port [16], or robotic-assisted. The steps are outlined in Fig. 13.1.

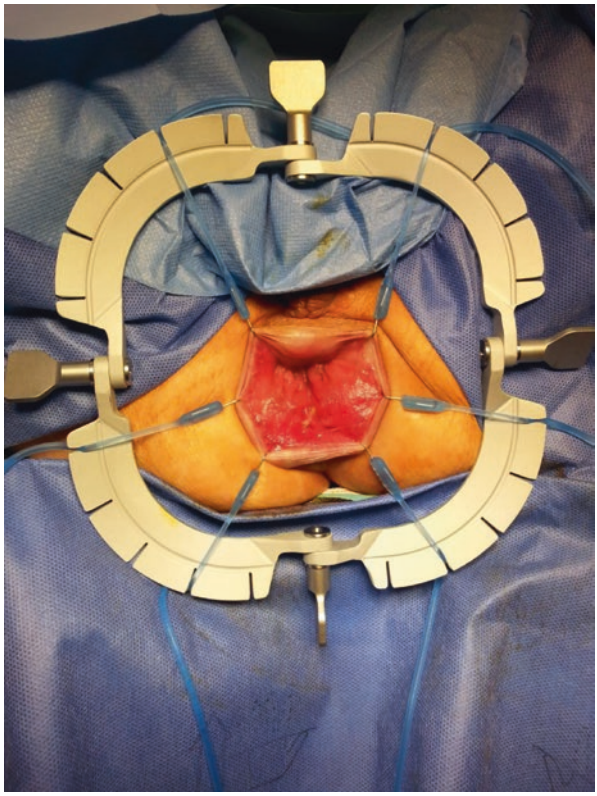

Fig. 13.1 Lonestar retractor® exposing anal mucosa

Operative Steps

Abdominal component
(Open/Laparoscopically assisted/Robotically assisted)

1. Lithotomy patient position
2. Mobilize left colon, including splenic flexure
3. Ligation of inferior mesenteric vessels
4. Continue dissection in TME plane inferiorly to pelvic floor, preserving hypogastric plexus.

Perineal component

1. Retraction using for example Lonestar retractor® (see Fig. 13.1)
2. Inject in sub-mucosal plane with diluted epinephrine for hemostasis and to facilitate dissection.
3. Incise mucosa and internal sphincter at least 1 cm distal from tumor
4. Anatomic dissection takes place in the in the space between internal and external anal sphincter.
5. The point at which dissection is started is dependent on the distal extent of the tumor (See Fig. 13.2)
   (a) Total ISR: Internal sphincter completely excised. Distal line of resection at intersphincteric groove.
   (b) Sub-total ISR: Distal line of resection between dentate line and intersphincteric groove.
   (c) Partial ISR: Distal line of resection at dentate line.
6. Continue dissection superiorly to meet the dissection from the abdominal component.
7. Specimen is delivered usually *per anum* and a colo-anal sutured anastomosis performed (straight anastomosis, J-pouch, transverse coloplasty)
8. The anastomosis is routinely defunctioned with a loop ileostomy.

Tumor Factors

Tumor Assessment

It is fundamental that pre-operative staging of tumors is accurate if considering ISR technique. This includes accurate assessment of tumor height, depth of invasion into local structures and distant spread. Pre-operative assessment of tumors is performed by a combination of clinical assessment with digital rectal examination/proctoscopy and radiological with endo-anal ultrasound and magnetic resonance imaging (MRI). In a systematic review of ISR comprising 14 studies and 1289 patients the mean distance of tumor was recorded as 31.1 mm proximal to the anal verge [13]. Most of the studies used tumors at least 30 mm from the anal verge as the cut off for ISR although

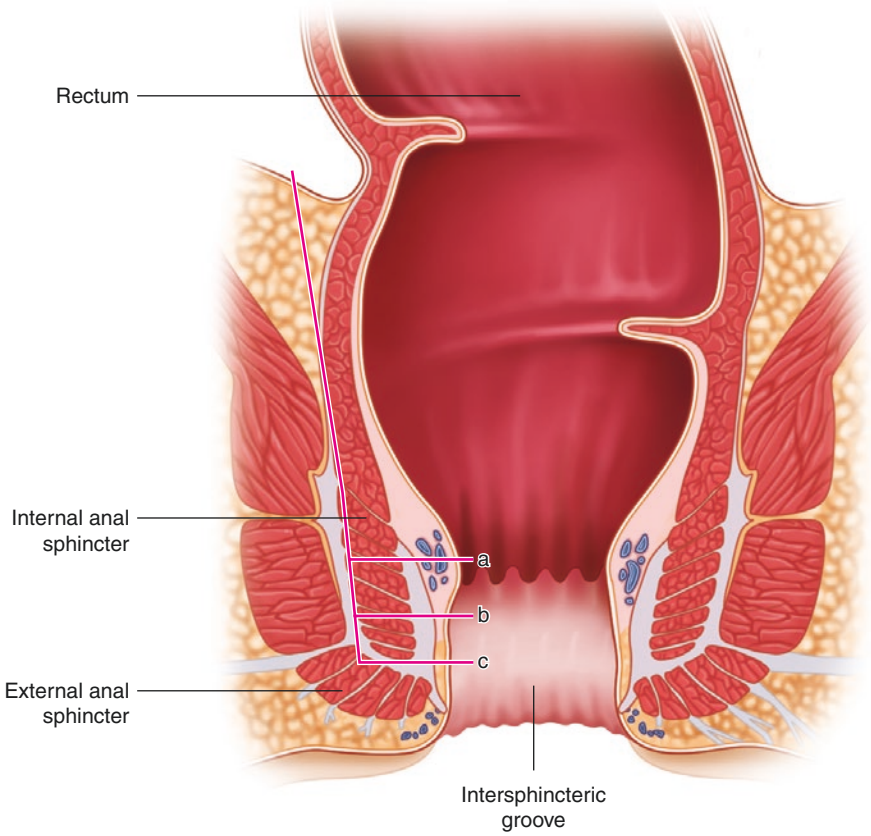

Fig. 13.2 Operative steps of intersphincteric resection (ISR) for rectal cancer. (**a**) Partial. (**b**) Subtotal. (**c**) Total

one study described management of tumors 15 mm from the dentate line [17]. The indications for ISR are often tumors within 1 cm of the anorectal ring. Contraindications for ISR are tumors invading levator ani, puborectalis and external anal sphincter and require APR if operable. Other contraindications for ISR include poorly differentiated tumors and distant metastatic disease. The majority of patients will have TNM stage 1–3 disease although there are some series with stage 4 disease [13].

Patient Factors

Patients with stomas have both an increased prevalence of depression [18] and report lower quality of life [19]. One of the main indications for ISR is the organ-preserving nature of the surgery and avoidance of a long-term stomas (91% are defunctioned with a temporary ileostomy [13]). Other considerations are cultural for example Muslims can be averse to having stomas and those with stomas report significantly reduced quality of life compared to non-Muslims independent of

where they live [20]. Specifically the issues surround prayer, ritual ablution, pilgrimage and fasting are problematic for Muslims and are often not identified by healthcare professionals who may not offer counseling appropriate to their patients' needs [21, 22]. Although the stigma has been improved by the use of Fatawās (a religious ruling on Islamic law by a recognized authority), Muslim patients may be motivated to seek a sphincter preserving operation for these reasons.

Patients that opt for ISR are likely to be a self-selected younger 'motivated' group with less co-morbidity and less aggressive tumor profiles. Patients with weak pelvic floors, the elderly population or through personal choice may prefer the 'control' that a permanent stoma provides.

Outcome Measurements

Pathological Outcomes

The histopathological assessment of specimens should be performed using standardized techniques [23]. A negative CRM is defined as tumor clearance of greater than 1 mm. ISR has good pathological outcomes with a large review demonstrating a CRM negativity rate of 96% (89–100) and R0 in 97% [13] (see Table 13.1). Mean local recurrence rate was 6.7% (0–23) [13]. The local recurrence rate is in keeping with a recent series of 189 patients, 124 of whom underwent partial or total ISR [6] (see Table 13.1), with local recurrence rates of 7.2% and distant recurrence rates of 20% compared to distant recurrence of 38% in those who had an APR. However, APRs represent a cohort of patients with lower, more aggressive tumor types and consequently worse pathological outcomes [24].

Morbidity and Mortality

Mortality rates in the post-operative period following ISR are low at 0.8% [13] – 2.4% [6]. Data regarding morbidity is reported with variable quality and using different classifications, and thus it is difficult to get accurate complication rates between series.

Table 13.1 Selected series and systematic review combining data from partial and total ISR

					5 Year				
Reference	Study type	n =	R0	Local recurrence (%)	OS (%)	DFS (%)	Mortality (%)	Morbidity (%)	Positive CRM
Martin et al. [13]	Review	1289	97	6.7	86.3	78.6	0.8	25.8	4%
Rullier et al. [25]	Series	186	NR	7	88.5	71.5	0	37.6 Dindo 3/4: 18.3	8.6%
Chau et al. [6]	Series	134	NR	7.2	NR	NR	2.3	NR	NR

NR not recorded

Anastomotic leak rates have been quoted as 9.1% in keeping with other rectal cancer series and anastomotic fistulas 2.2% [13]. Others included wound complications of 2.7% and bleeding 1.4%. The 5-year overall and disease-free survival is 86.3% and 78.6% in one review [13] and 88.5% and 71.5% in a large series [25] (see Table 13.1).

Functional Outcome and Quality of Life

Functional data are reported with different outcome measures in published series including factors like bowel motions per 24 h and a range of scoring systems such as Jorge & Wexner continence score, Kirwan classification, Mayo clinic tool etc. In the a large review, 8 out of the 14 included studies reported functional outcomes [13]. Mean average number of bowel movements per 24 h was 2.7 (2.2–3.7), perfect continence in 51.2% (32.7–86.3) and fecal soiling experienced by 29.1% (11–63) of patients post ISR. (see Table 13.2).

Neoadjuvant chemoradiotherapy (CRT) decreases local recurrence rate in patients undergoing ISR but may impact on functional outcomes. Pre-operative radiotherapy potentially can damage the sphincter apparatus and nervous supply reducing anorectal function [27]. Several studies have demonstrated a reduction in anorectal function, lower maximal squeeze pressures, worsening of Wexner scores [28] and poorer continence scores [29] in receiving neoadjuvant CRT before sphincter-preserving proctectomy.

ISR impacts on bowel function and although this data is not published in all series informing patients of these facts is a very important part of the consent process.

Core Outcome Datasets and Patient Reported Outcomes

A major criticism leveled at surgical research is the lack of consistency in terms of recorded outcomes. A systematic review of randomized and non-randomized studies of outcomes following colorectal surgery identified 766 different recorded

Table 13.2 Functional results of systematic review by Martin et al. and study by LaForest et al. comparing pelvic rehabilitation group vs. control

	n =	Stool frequency per 24 h	Perfect continence (%)	Fecal soiling (%)	Incontinence to flatus (%)	Urgency (%)	Anti-diarrheal medication (%)
Martin et al. [13]	727	2.7 [2.2, 3.1]	51.2 [35.4, 67.1]	29.1 [15.3, 43.0]	23.8 [16.7, 30.9]	18.6 [6.7, 30.5]	18.4 [20.8, 57.6]
Laforest et al. (pelvic rehabilitation group) [26]	22	2.6 (1–6)	18%	18%	27%	36%	55%
Laforest et al. (control group)	24	4 (1 10)	13%	12%	29%	38%	50%

clinical outcomes with lack of consistency and poor definitions of terms [30]. This makes comparing research from different sources challenging and selective reporting of outcomes can lead to outcome reporting bias [31]. There is a drive towards the formation of core outcome datasets dependent on the area of research, these datasets stipulate both standard data points to be recorded such as demographic information and much more detailed specific data points appropriate to the subspecialty [32].

This can be even more difficult when patient reported outcomes are measured due to the heterogeneity of symptoms and how they are reported and recorded. The most common technique for recording patient reported outcomes is through questionnaires, but even if validated, they have been developed by different disciplines with different agendas [33]. Methodology exists to identify patient reported outcome domains from the plethora of disparate patient reported outcome measures [33]. This is an area for future development in the field of colorectal surgery including rectal cancer surgery.

Discussion

There is a trend towards sphincter-preserving surgery with recent series and papers presenting reasonable patient and oncological outcomes [13]. Overall and disease-free survival are reported at almost 90% and 70% respectively, but sphincter-preserving surgery is not a new phenomenon. Cuthbert Dukes and Heinrich Westhues in the 1930 and 40s performed the seminal research investigating the pathological spread of rectal malignancies that provided evidence for radical sphincter preserving surgery [34, 35]. Golligher gave his Hunterian lecture entitled 'Functional results after sphincter-saving resections of the rectum' back in 1951 [36]. Low rectal cancer is a challenging area of surgery with the need for excellent decision making and patient counseling to decide on the optimal management plan. This needs to balance oncological outcome, whether to perform sphincter preserving surgery and the function and quality of life this allows. There is evidence that patients will defer decision-making regarding sphincter preserving surgery or APR to their surgeon [37].

ISR can be performed safely by a variety of means and has comparable oncological outcomes in published series. Most surgeons use the technique as published by Schiessel and colleagues [14] but there is variability in the type of coloanal anastomosis performed. This to a certain extent will depend on whether a total, sub-total or partial ISR is being performed. A straight hand-sewn anastomosis has the advantage of facilitating dilatation of the new reservoir. A colon J-pouch can provide increased reservoir function that may improve patient outcomes. Several papers suggest that a J-pouch anastomosis gives patients better function, reduced stool frequency and less urgency compared to a straight anastomosis but these effects are not sustained long-term [38].

The data presented regarding patient outcome measures is heterogeneous with variable results. A review of over a 1000 patients found that stool frequency of 4–5 per day was present in 12–57% and day/nocturnal soiling in up to a third [39]. Interestingly despite the high stool frequency and soiling patient satisfaction was rated at 71% [39]. Fecal incontinence-related quality of life scores are lower in ISR compared to low anterior resection but global quality of life scores are similar. One study reported the outcomes from 5 year follow up demonstrating imperfect function and yet satisfaction was greater than 90% [40].

One area that may improve patient outcomes is the use of pelvic floor rehabilitation commonly used for patients with weak pelvic floors and incontinence. Anal sphincter rehabilitation has proved successful in improving quality of life vitality and mental functioning subscales of the SF-36 health status questionnaire and fecal incontinence quality of life score [26]. Those receiving rehabilitation had significantly lower stool frequency but continence scores and other outcome measures were no different compared to control (see Table 13.2). This was in a small cohort of 22 patients in the treatment group undergoing sphincter preserving laparoscopic TME resections for rectal cancer, of which 15 patients had ISR. This is an interesting area for future research to delineate if pelvic floor rehabilitation is a useful adjunct to lower rectal surgery.

In conclusion ISR represents a specialist procedure suitable for a small group of motivated patients that have are likely to be younger with reasonable pelvic floor function. Areas for future development include standardized recording of core and patient outcomes and the potential benefits of pelvic floor rehabilitation for quality of life.

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Chapter 14
The Changing Face of Abdominoperineal Excision

Charles Sabbagh, Francois Mauvais, and Jean-Marc Regimbeau

Introduction

Although there are ever fewer indications for abdominoperineal resection (APR), preservation of the sphincter or rectum during tumor resection is still an important objective [1]. In fact, R0 resection of advanced tumors in the low rectum sometimes requires the anus to be sacrificed (particularly in cases of sphincter or puborectalis invasion) [2]. In this context, APR becomes an oncological and technical challenge.

The outcomes of standard APR techniques have been poor: rectal perforation and circumferential margin involvement are frequent, the local recurrence rate is 15–30% and so the 5-year survival rate is low [3, 4]. For these reasons, groups from Sweden and the United Kingdom have recently published encouraging results for a radically new technique called extralevator APR (ELAPE) [5]. Technical progress in other areas (including laparoscopy, perineal reconstruction and rehabilitation) has helped to improve postoperative recovery. The objectives of this chapter are to (i) understand the oncological and technical problems that occur during standard APR, (ii) discuss the current indications for APR when seeking to obtain R0 resection, (iii) report on the latest technical modifications available to the colorectal surgeon and (iv) described the associated results.

C. Sabbagh · J.-M. Regimbeau
Department of Digestive Surgery, Amiens University Hospital, Amiens, France

F. Mauvais (✉)
Department of Digestive Surgery, Beauvais General Hospital, Beauvais, France
e-mail: f.mauvais@ch-beauvais.fr

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Factors Influencing the Prognosis After Abdominoperineal Resection

Whether measured in terms of local recurrence or survival, the oncologic outcomes after APR are worse than those for anterior resection (AR). Heald et al. were the first to note the poor prognosis for these patients – even when total mesorectal excision (TME) was correctly performed – and emphasized that most APRs were performed for the most advanced cases of rectal cancer [6]. Other retrospective studies of TME with prospectively gathered data confirmed these findings. Marr et al. suggested that the high rate of circumferential margin involvement was a possible explanation. Two large, prospective studies (in Norway and The Netherlands) confirmed the poor prognosis associated with APR and found that both circumferential margin involvement and intraoperative perforation were independent risk factors in a multivariable analysis [3]. Nagtegaal et al. observed that the muscle, submucosa or even the mucosa was penetrated during dissection in more than one third of patients and argued that a different technique was required [4].

The poor prognosis associated with APR may be linked to tumor-related factors (size, site and stage) and/or technical factors (inadequate resection and technical errors).

Tumor-Related Factors

Tumor Size

Tumor size is an independent prognostic factor in rectal cancer. Patients requiring APR are often those with large, voluminous tumors. It is therefore possible that the poor prognosis associated with APR is related to the TNM stage. Chambers et al. compared the oncologic outcomes of APR and AR in patients with low rectal cancer undergoing surgery between 1993 and 2004. However, the two groups of patients differed significantly at baseline, since there were more advanced T stage tumors in the APR group. The outcome was worse for APR, in terms of both the R1 resection rate (25.7% vs. 6.5% for APR and AR, respectively) and the 5-year survival rate (55% vs. 67%, respectively; $p = 0.05$) [7]. In a retrospective study, Kim et al. found that relative to a sphincter-preserving procedure, APR was associated with a lower 5-year cancer-specific survival rate (52.9% vs. 71.1% respectively) and a higher recurrence rate (22% vs. 11.5%, respectively) in patients receiving neoadjuvant chemoradiotherapy for low rectal cancer (less than 6 cm from the anal verge), even though there was no statistically significant intergroup difference in the tumor stage distribution, with 67% of sphincter preservation patients with ypT3-T4 tumors [8].

Tumor Site Within the Lower Rectum

The tumor site within the lower rectum also appears to influence the prognosis. Wibe et al. found that relative to tumors of the middle and upper rectum, lower rectal tumors were more often T4 (13% vs. 7%, respectively) and less likely to be well-differentiated (14% vs. 7%, respectively) [9]. It is also possible that lymph node extension to the pelvic walls [10] and predisposition to pulmonary metastases are predictive of a poor prognosis in this setting [8].

Response to Neoadjuvant Therapy

At present, low rectal cancers initially scheduled for APR can be treated with neoadjuvant therapy and then sphincter-preserving AR [11]. Sphincter preservation is possible only if the tumor has an objective response to chemotherapy. In the absence of an objective response or down-staging, the oncologic outcome is poor [12]. These patients are probably the best candidates for APR. In this setting, the prognosis depends more on the tumor profile than on the technique employed.

Technical Factors

Perforation

Eriksen et al. found that the rectal perforation rate was significantly higher in APR than in AR. Moreover, the researchers showed that local recurrence rate was correlated with perforation (28.8% in cases of perforation vs. only 9% in its absence) [13]. The prospective studies performed in Norway and the Netherlands yielded similar conclusions. Perforation usually occurs in the anal canal (in 74% of cases) when dissection is too close to the tumor or excessive traction is used to obtain sufficient exposure (particularly for the posterior aspect of the rectum) [4].

Circumferential Margin

The circumferential margin is a major prognostic factor in rectal cancer [14, 15]. During APR, invasion of the circumferential margins is related to the same factors that lead to perforation (i.e. dissection too close to the tumor) but perhaps also to the difficulty of performing non-mutilating R0 resection when the tumor is voluminous. Although resection of the posterior wall of the vagina is usually not a problem, resection of the prostate or the lower portion of the sacrum is challenging. The need to obtain a clean margin is the prime technical objective. When patients have an

adequate circumferential margin, the prognosis does not differ according to whether APR or AR is performed. In the above-mentioned Dutch study, the prognosis of APR and AR patients not receiving neoadjuvant chemoradiotherapy were similar as long as the circumferential margin was not involved (local recurrence: 8.6% vs. 9.2%, respectively; 5-year survival: 70.7% vs. 72%, respectively) [4]. Hence, APR must be performed with respect to optimal oncologic principles: adequate lateral and distal clearance is needed to avoid the risk of perforation and circumferential margin involvement.

Technical Problems Occurring During Standard APR

Several problems related to the quality of rectal excision can arise during APR: the tumor's proximity to organs (prostate, levator ani), poor visibility during deep pelvic dissection via an abdominal approach, poor perineal exposure, and the extent of the perineal defect in major resections. A better understanding of these difficulties should prompt a number of technical modifications.

Anatomy

The mesorectum of the upper and middle rectum is fairly thick and forms a "safety zone" between the dissected area and the tumor [16]. However, this protective tissue is absent in the lower rectum, where the digestive tract is directly in contact with Denonvilliers' fascia or the vagina anteriorly, the rectosacral fascia posteriorly, and the puborectalis and iliococcygeal components of the levator ani muscle laterally. During dissection of the lower rectum from above, the initial dissection plane (near the upper rectum) is in contact with the mesorectal fascia and leads to the rectal muscularis below, which is not protected by the mesorectum. To avoid touching the tumor, it is necessary to resect the anatomic structures in contact with the muscular wall of the lower rectum. The rectosacral fascia must be separated from the presacral fascia (near S3-S4) posteriorly, from Denonvilliers' fascia anteriorly and from the surface of the levator ani muscle laterally [17, 18].

Poor Visibility During Deep Abdominal Dissection

When mobilizing the lower rectum during laparotomy, distal dissection is hindered by several factors: the pelvis is narrow, the sacrum is concave, the lower rectum is obscured by the anterior pelvic organs, and, in the male pelvis, the anterior aspect of the last few centimeters of the rectum is hidden by the tip of the prostate. All

these factors result in blind dissection of the very lowest part of the rectum, with an elevated risk of tumor perforation [19].

Poor Perineal Exposure

During conventional APR, the patient lies in the lithotomy position. The anterior perineum interferes with anterior dissection, even when the thighs are spread as widely as possible. Posterior dissection is also obstructed by the posterior perineum, which obliges the surgeon to work from bottom to top and not (more logically) from top to bottom; this leads to poor visibility and restricted movement. Poor exposure might also explain why 62% of the perforations associated with APR occur during perineal dissection [20].

Insufficient Resection

After broad rectal excision, the musculocutaneous defect can be quite large – making perineal closure difficult or impossible. To avoid this problem, surgeons sometimes try to preserve the levator ani muscle. However, dissection too close to the tumor may then create a "Morson's waist" defect [21]. Holm et al. explained that in conventional APR, the risk of perforation is greatest during the perineal approach (while dissecting close to the levator ani muscle prior to resection) [5] (Fig. 14.1).

Perineal Wound Healing

Perineal wound healing is often difficult or delayed. Primary perineal closure is fraught with difficulties, and complication rates can be as high as 40% [22] (due mainly to wound dehiscence and perineal infection). Chemoradiotherapy also delays perineal healing and promotes perineal infection.

Current Indications for APR

The role of APR in the management of low rectum adenocarcinoma is currently limited to tumors that respond poorly to neoadjuvant therapy and are therefore not amenable to sphincter-preserving strategies. The oncologic justification for performing APR in lower rectum tumors is related to situations in which the basic tenets of safety cannot be applied during AR or intersphincteric

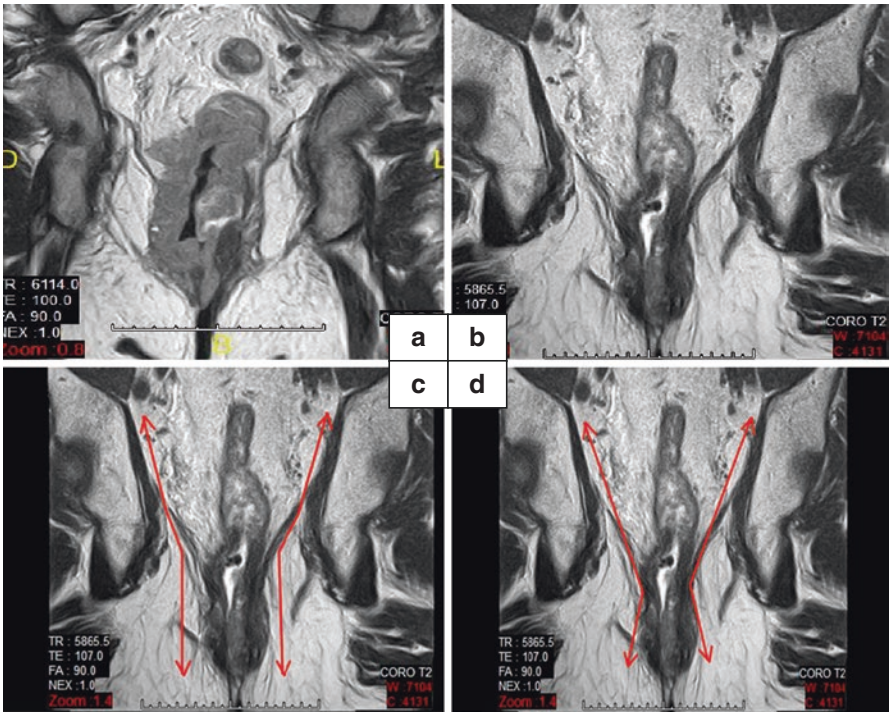

Fig. 14.1 (**a**) A low rectal tumor, with an extension to the levator ani on both sides (before chemoradiotherapy). (**b**). A low rectal tumor, with persistent extension of the tumor to the levator ani after chemoradiotherapy. (**c**) Planes of the extralevator APE. (**d**) Planes of the standard APE, leading to tumor perforation and an R1 resection

anoproctectomy (or intersphincteric resection): tumor involvement of the external sphincter or pelvic floor (levator ani), and circumferential margins estimated preoperatively to be less than 1 mm. A recent study found that APR was performed in only 15% of cases of low rectal cancer [23]. Other situations may prompt the use of APR in patients who could not undergo AR because of (i) sphincter incompetence, (ii) the risk of poor functional outcomes in the elderly or (iii) poor colonic vascularization that might compromise a low colorectal or coloanal anastomosis.

Modern APR Techniques: Principles and Key Points

The goal of APR is to achieve R0 resection. To this end, one must have high-quality preoperative pelvic imaging data [24]. In particular, magnetic resonance imaging (MRI) is the rectal surgeon's roadmap. It provides information about the tumor's

upper border, sphincter or puborectal invasion and the anterior extension of very voluminous tumors, enables surgical planning and predicts the need to resect prostatic or vaginal tissues and the endangered side [25].

Principles of ELAPE

In APR, the objective is to (i) achieve an R0 resection that is not too close to the tumor, and (ii) perform an extensive cylindrical excision without opening up the space between the tumor and the levator ani. This requires good exposure of the perineum (in the prone position), replacement of the lost perineal tissues (omentoplasty) and efforts to promote rapid recovery (mainly via the use of laparoscopy and antalgics).

The Abdominal Approach

The abdominal approach follows the general rules of rectal resection. The main difference is that abdominal dissection is stopped before reaching the anatomic plane between the lower part of the mesorectum (near the tumor) and the levator floor. Abdominal dissection should stop near S2 posteriorly, at the level of the pelvic plexus laterally and just below the bladder or the uterine cervix anteriorly [5]. In this manner, the levators are not exposed and the abdominal dissection remains high and thus distant from the tumor. The tumor and levator are resected as a single block during the perineal approach. Omentoplasty is still indicated for filling the pelvic cavity and accelerating perineal healing [26]. The abdominal approach ends with extraperitoneal colostomy and pelvic drainage [27].

The Perineal Approach

The goal here is to excise the portion of levator muscles that was not removed during the abdominal part of the operation. After anal closure, the perianal incision starts at the low sacrum. Dissection continues around the external sphincter until the exopelvic aspect of the levator ani (out to the lateral wall of the pelvis, i.e. the muscle's tendon insertion) is completely exposed. This maneuver requires active retraction of the gluteus maximus muscle (to expose the levator ani as much as possible) and then dissection and division of the presacral fascia (high enough to locate the trans-abdominal dissection). When the patient is lying in the prone position, disarticulation of the coccyx sometimes provides better exposure and easier presacral division (Figs. 14.2 and 14.3). The levator muscles are then divided in contact with the pelvic wall. Anterior dissection is more challenging in men: overly anterior dissection can result in unwarranted mobilization of the bladder and prostate, and there is also a risk of injury to the membranous portion of the urethra.

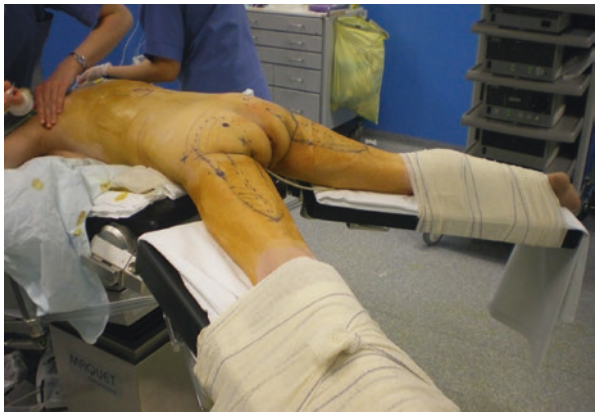

Fig. 14.2 Prone position for the perineal dissection offers a good exposure for pelvic dissection

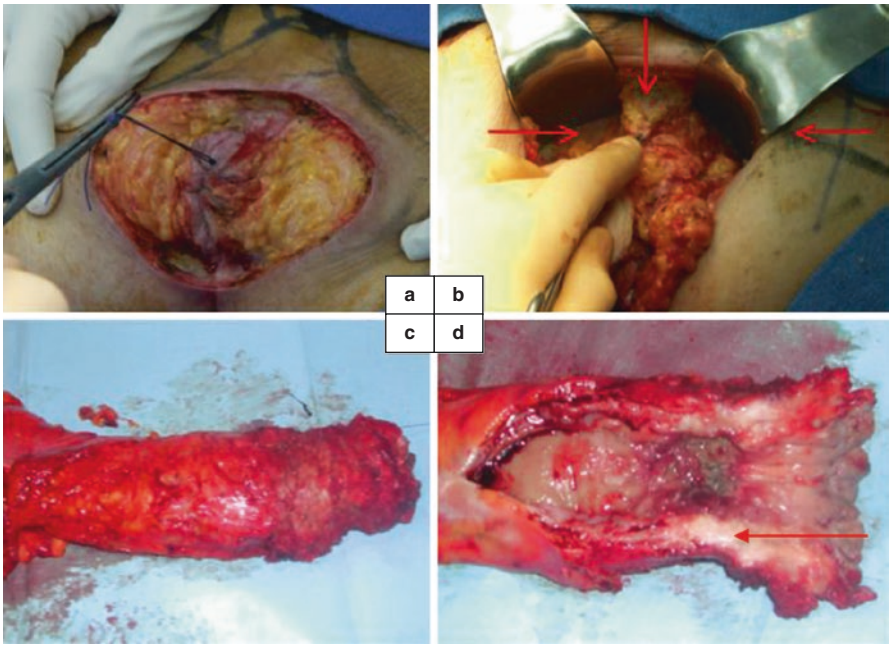

Fig. 14.3 (**a**) Cutaneous excision of the pelvic dissection. (**b**) The coccyx, which can be disarticulated during dissection. The retractors are exposing the exopelvic fascia of the levator ani behind the gluteus major. (**c**) A proctectomy specimen without a cone effect, after extralevator abdominoperineal excision. (**d**) Surgical specimen with tumor ulceration and tumor involvement of the sphincters

To limit these risks, it may be necessary to use a rigid urinary catheter to locate the urethra or to start dissection in the midline (until contact with the prostate is established) before pursuing the dissection laterally. Dissection along the posterior aspect of the prostate leads to the abdominal dissection, anterior to Denonvilliers' fascia. When the tumor is located anteriorly, the dissection plane runs through the prostate in males (with the removal of 5–10 mm of prostatic tissue. In females, the posterior wall of the vagina is resected [5, 28]**.**

In order to perform this resection, several choices must be made: the abdominal approach, the patient's position for the perineal dissection and reconstruction of the perineal defect.

Options

Laparoscopy Versus Laparotomy

Randomized, controlled trials in patients with colon cancer have shown that compared with open surgery, laparoscopy is associated with less postoperative pain, faster recovery, better health-related quality of life and similar survival rates [29]. For rectal cancer, the COLOR II trial is an ongoing non-inferiority study of local recurrence at 3 years. At the time of writing, only the short-term outcomes have been published. They show a better recovery after laparoscopic TME, with similar safety, resection margins, completeness of resection and preservation of urinary and sexual function when compared with open surgery [30, 31]. Twenty-three percent of the patients in the open surgery group and 29% of those in the laparoscopy group underwent APR but a subgroup analysis has not been performed. In 2014, Ng et al. published the results of a randomized, controlled trial comparing the short-term outcomes of open vs. and laparoscopic-assisted TME with sphincter preservation. Postoperative recovery was better after the laparoscopic-assisted TME, with less requirement for antalgics ($p < 0.001$), earlier mobilization ($p = 0.001$), a lower short-term morbidity rate ($p = 0.043$) and a non-significant trend ($p = 0.071$) towards a shorter length of hospital stay. Moreover, oncologic clearance (in terms of the macroscopic quality of the TME specimen, circumferential resection margin involvement, and the number of lymph nodes removed) was similar in the two groups [32]. To the best of our knowledge, no randomized, controlled trials have focused on APR.

From a technical standpoint, the laparoscopic approach does not change the surgical plan. However, two points must be underlined. Firstly, a laparoscopic approach makes it difficult to perform a colostomy below the peritoneum. Secondly, the trocar must be carefully inserted, in order to avoid epigastric vessel injury (particularly when a rectal flap is to be used).

In summary, the results of the COLOR II trial and trials in colon cancer suggest that the laparoscopic approach is safe for rectal cancer.

Which Position Should Be Used for Perineal Dissection? The Lithotomy Position or the Prone Position?

In standard APR, the patient lies in the lithotomy position (supine, with the thighs spread and the buttocks clear of the operating table). This position is practical because it does not require any major adjustments when the surgeon moves from the abdominal field to the perineal field. The main disadvantage is that the posterior perineum is "under the patient" and so clear exposure of the operating area is not

available. Contrary to normal practice, dissection must be posterior to anterior. Holm et al. have suggested that the prone position (used for the trans-sacral route popularized by Kraske [33] and transanal excision of superficial anterior tumors of the rectum) is suitable for APR [5]. Although the prone position has many constraints, it provides optimal exposure of the posterior perineum. With the patient in the prone position, a sandbag is placed below the anterosuperior iliac spines and the pubis, and another is used to raise the shoulders and thorax. The legs can be placed in stirrups and spread in a V-shape, allowing the surgeon to operate from between the legs. The table is folded at the waist to give the "prone jackknife position", which lifts the posterior perineum and provides a direct view of the operating field (Fig. 14.2). This position facilitates dissection of the levators, the coccyx and the presacral space but does not interfere with dissection of the anterior perineum. The major disadvantage of prone position is the need to complete the abdominal stage before changing to the perineal approach. Furthermore, the operating time is longer because of the change in position; there is risk of compression of the vena cava or of rhabdomyolysis if the position is inappropriate. Lastly, our personal experience indicates that the prone position is not a contraindication to use of a rectal flap. In their initial report on ELAPE, Holm et al. described the performance of perineal dissection in the prone position [5]. Since then, many surgeons have questioned this approach by arguing that changing the patient's position is time-consuming and may be associated with specific complications.

In 2008, the UK group reported on the outcomes associated with the prone position. The tumor perforation rate was significantly lower in the prone position than in the lithotomy position (6.4% vs. 20.6%, $p = 0.027$). The main limitation of this study is that it compares the outcomes of standard APR in the lithotomy position with those of ELAPE in the prone position [34]. These findings were confirmed in a retrospective series by Anderin et al. in 2013. The researchers observed a significantly lower perforation rate for the prone position (4% vs. 12% for the lithotomy position; $p = 0.001$). The main limitations of this work are that the proportion of patients having undergone preoperative neoadjuvant treatment was significantly higher in the lithotomy group than in the prone group (23.5% vs. 11.2%, respectively; $p < 0.001$) and that the resection of other organs was more frequent in the prone group than in the lithotomy group (26.5% vs. 16.1%, respectively; $p = 0.007$) – making it difficult to interpret the data on perforation rates [35].

Three other studies compared the outcomes of the prone and lithotomy positions and found no differences in the perforation rate. De Campos-Lobato et al. reported a perforation rate of 2.4% in the lithotomy position and 4.6% in the prone position ($p = 0.5$), and Tayyab et al. reported rates of 5% and 4.6%, respectively, ($p = 0.43$) [36]. Ortiz et al.'s propensity score analysis compared conventional APR (in the lithotomy position) with ELAPE (in the prone position) found perforation rates of 7.7% and 7%, respectively; $p = 0.7$ [37].

Another parameter of interest when comparing the lithotomy and prone positions is the incidence of circumferential margin involvement. Three studies have reported this data. De Campos-Lobato et al. found values of 8.5% vs. 2.3% for the lithotomy and prone positions, respectively ($p = 0.17$) and Tayyab et al. found

Table 14.1 Rates of rectal perforation and circumferential margin involvement during perineal dissection, stratified by patient position

Study	Lithotomy position	Prone position	p
Perforation			
West et al. [34]	20.6%	6.4%	0.027
Tayyab et al. [38]	5%	3.4%	0.5
de Campos et al. [36]	2.4%	4.6%	0.43
Anderin et al. [35]	12%	4%	0.001
Ortiz et al. [37]	7.9%	7.7	0.9
CRM* involvement			
Tayyab et al. [38]	27%	27.6	0.55
de Campos et al. [36]	8.5%	2.3%	0.17
Ortiz et al. [37]	13.1%	13.6%	0.8

CRM circumferential resection margin

values of 27% and 27.6%, respectively [36, 38]. In the propensity score analysis, Ortiz et al. did not find any difference in circumferential margin involvement (13.1% and 13.6% for the lithotomy and prone positions, respectively; p = 0.8) [37] (Table 14.1). However, the main limitation of this study is that the type of resection (R0, circumferential margin invasion), the quality of mesorectal excision and the pathological TNM stage were included in the propensity score. The main criticism of standard APR is the high rate of R1 and circumferential margin involvement, and so the data in Ortiz et al.'s study cannot be used to analyze the impact of ELAPE (relative to standard APR) on oncological outcomes [37]. This latter analytical technique has some serious methodological issues and the results are subject to debate.

In conclusion, the prone position does not provide oncological benefit. However, we consider that it enables better exposure and thus favors good dissection – particularly in cases of anterior lesions. However, the lithotomy position is preferable for fragile patients or in the absence of puborectalis invasion.

Reconstruction

Historically, the perineum has been left open and then packed to support the perineal floor and promote hemostasis and drainage [39]. However, this technique resulted in significant patient discomfort and delayed wound healing (four or more months). Today, direct closure involves closing the perineum (when possible), filling the pelvic dead space with omentum and draining the pelvic cavity with transabdominal, active, closed suction drains. However, the healing rate remains low under certain conditions. In a series of 210 patients who underwent ELAPE, Bebenek et al. reported that 12.9% had minor wound complications and 4.8% had major complications [40]. Combining omentoplasty with primary closure might limit the dead space and limit small bowel adhesion to the pelvis. A review of 10

studies by Nilsson et al. reported a minor infectious complication rate of 4–28% and a primary healing rate at 3 months of 87–100% [26].

The efficacy of mesh application for abdominal wall reconstruction has prompted the use of these materials in perineal reconstruction. Absorbable and non-absorbable meshes have therefore been used to separate the abdominal cavity from the perineal defect, prior to direct skin closure. A recent review identified 12 studies in which biological mesh was used for perineal closure. In a pooled analysis, a total of 149 patients underwent ELAPE and pelvic floor closure with either porcine dermal collagen (Permacol™) (n = 101), porcine small intestinal submucosa (surgiSIS®) (n = 19), human acellular dermal matrix (n = 12) and cross-linked acellular porcine dermal collagen (n = 17). On average, 68.5% of the patients had undergone neoadjuvant radiotherapy. Short- to medium-term follow-up identified 41 (27.5%) minor wound complications, 20 (13.4%) major wound complications and 4 (2.7%) perineal hernias. Two cases of small bowel obstruction were considered to be associated with the use of Permacol™ mesh [41].

Myocutaneous flaps are thought to be beneficial by enhancing the healing process and reducing the pelvic dead space. Several types of myocutaneous flap have been described: gluteal flaps, rectus abdominis flaps, gracilis flaps, and superior and inferior gluteal artery perforator flaps.

A gluteus flap was used in 28 patients in the original study by Holm et al. There were four (14%) flap-related complications [5]. Chan et al. compared primary closure (n = 21) and a vertical rectus abdominis muscle flap or a gracilis flap (n = 30). There were four (19%) major complications in the primary closure group and five (16%) in the flap group [42].

Inferior gluteal artery perforator (IGAP) flaps and superior gluteal artery perforator (SGAP) flaps are commonly used in breast reconstruction [43]. These perforator flaps have been used as pedicle flaps for the surgical management of sacral pressure ulcers [44] and pilonidal sinus [45]. Wagstaff et al. [46] described their use for vaginal reconstruction in 14 patients (11 SGAP flaps and 3 IGAP flaps). The choice between an SGAP flap and an IGAP flap for perineal reconstruction depends on the perforator site and the preoperative color Doppler assessment [47, 48]. Although the IGAP flap appears to be generally more suitable, a satisfactory perforator from the superior gluteal artery can equally be used. In such a case, the selected perforating vessel must then be dissected through the muscle fibers up to its origin on the gluteal artery. This procedure provides a more mobile paddle and makes it easier to reach the reconstruction target. It is often necessary to transect several muscle fibers in order for the flap to reach the perineal defect and prevent the perforator from being stripped off by muscle contraction. Skin flaps are de-epithelialized and placed into the perineal defect to fill the dead space. To avoid this dissection and limit the risks of pedicle damage, Boccola et al. [49] described a myocutaneous flap based on the inferior gluteal artery but which involved only the medial fifth of the muscle (containing the perforating vessel supplying blood to the skin paddle). This flap is a compromise for the gluteal region, as the muscle-sparing vertical rectus abdominis musculocutaneous flap is for the abdominal region (Fig. 14.4).

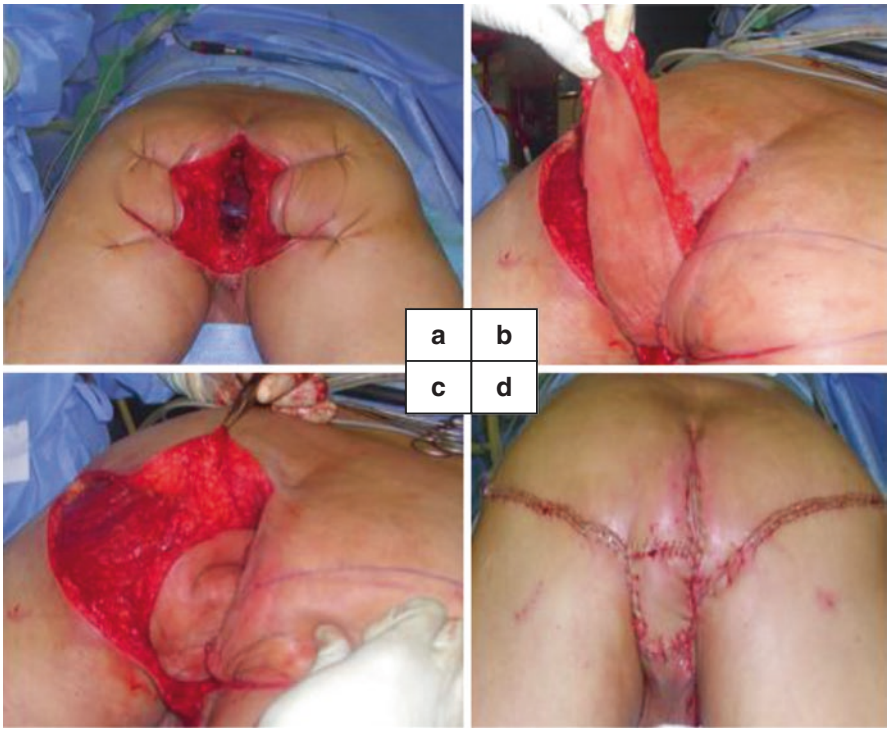

Fig. 14.4 (**a**) The perineal defect before closure. (**b**). Harvesting of a myocutaneous flap. (**c**) Insertion of the myocutaneous flap into the pelvis. (**d**) The appearance of the perineum after closure

In conclusion, the best way to close the perineum is not yet clear, although the perineal cavity must be filled.

Short and Long-Term Outcomes

Short-Term Morbidity

There are few published data on specific postoperative morbidity after ELAPE. In 2012, Vaughan-Shaw et al. compared the short operative outcomes and quality of life in 16 patients having undergone ELAPE, 10 patients having undergone laparoscopic standard APR and 10 patients having undergone open standard APR. There were no significant intergroup differences in terms of the duration of intravenous fluid therapy, the number of days until stoma competence, and the median length of stay. A shorter time until a trial without a urinary catheter ($p = 0.02$) was noted in

the ELAPE and laparoscopic APR groups, along with a trend towards less use of patient-controlled analgesia and anti-emetics. In all, nine patients experienced perineal wound complications. Eight of the patients received neoadjuvant therapy and two underwent ELAPE [50]**.** In the same year, Dalton et al. reported on the short-term outcomes of 31 ELAPE procedures; the researchers reported a 30-day mortality rate of 6.6% but did not give any details of the causes of death [51]. The best-quality evidence for postoperative morbidity comes from the multicenter propensity score-matched analysis of standard APR (n = 457) and ELAPE (n = 457). There were no intergroup differences in terms of postoperative complications (52.3% vs. 48.1% for APR and ELAPE, respectively; p = 0.2), perineal wound problems (26% vs. 21.9%, respectively; p = 0.14), the need for reoperation (7.7% vs. 7%, respectively; p = 0.7) and postoperative death (2% vs. 2%, respectively; p = 1) [37].

Despite extensive resection, ELAPE does not appear to be associated with an increased risk of postoperative complications (relative to standard APR).

Long-Term Outcomes

The study by Dehni et al. concerned 106 APRs for low rectal adenocarcinoma performed between 1992 and 1997 [52]: 33% were for stage III tumors and 12% were for stage IV. Forty-four percent of the patients had received neoadjuvant radiation therapy. The technique described by Dehni et al. corresponds to a cylindrical excision and the paper clearly indicates that the space between the tumor and the levator muscle was not entered. The intraoperative perforation and circumferential involvement rates were not provided. The local recurrence rate was low (10%, after a median follow-up period of 55 months).

Holm et al. reported the long-term outcomes in 193 patients. The estimated cumulative incidence of local recurrence at 5 years was 6%. In three of the patients having developed a local recurrence, the surgical specimen had a perforation. Furthermore, the circumferential margin was positive in seven patients. In the remaining five patients, there was no obvious reason for the local recurrence. Seven patients with local recurrence also had distant failure. Distant metastases were diagnosed in 61 (33%) patients. The estimated overall 5-year survival rate was 60% and the cancer-specific survival rate was 67% [53]. The main limitation of these data is that there are no comparisons with standard APR.

In the multicenter propensity score-matched analysis, Ortiz et al. reported a 2-year recurrence rate of 2.7% after standard APR and 5.6% after ELAPE (p = 0.6), however methodological limitations with the propensity-score matching technique are described earlier in this chapter.

Although few data on long-term outcomes after ELAPE are available, the results of most studies suggest that the technique is associated with lower rates of perforation and circumferential margin involvement. Given the limited follow-up of patients and the relatively recent implementation of the technique, no data on a putative reduction in local recurrence are currently available.

Conclusion

The indication for APR is becoming narrower, and the technique is only applied in perhaps 10% of cases of low rectal cancer. When APR is necessary, R0 resection is essential, which often requires sphincter or levator ani resection. To perform extensive resection, (i) good exposure is essential and (ii) use of the prone position (when possible) ensures a clear view of the danger zone. ELAPE is a means of obtaining an R0 resection, rather than being a goal *per se*. The best technique is probably a limited levator resection of the invaded area on the basis of the MRI imaging, although this is currently a difficult procedure. Hence, a standardized technique is required, and ELAPE is more likely to yield adequate excision.

Laparoscopic approaches and reconstruction are helpful in limiting postoperative complications and discomfort. Although there may be strong arguments in favor of a laparoscopic abdominal approach, the choice of reconstruction is more difficult. Gluteal perforator flaps enable the resection area to be filled with well-vascularized tissues, with minimal defects in the native donor area and the preservation of muscle tissue.

APR should be considered as an oncologic challenge in dealing with advanced tumors of the lower rectum, rather than a failure of sphincter-preserving approaches. However, obtain the best oncologic result and faster wound healing requires surgical expertise and collaboration with plastic surgeons to quickly offers oncologic medication if necessary.

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Chapter 15
Neorectal Reservoir Construction: Techniques and Outcomes

Osama Al-Bermani, Pranavan Palamuthusingam, and Yik-Hong Ho

Introduction

The first operation that allowed patients with proximal third rectal cancer to avoid a permanent stoma was the anterior resection performed by Dixon in the 1940s. Following this, the coloanal anastomosis was proposed for patients with low rectal cancers which permitted sphincter preservation with variable anal continence and which was regarded as superior to the abdominoperineal resection (APR). Over the past three decades, there has been remarkable progress made in the management of rectal cancer which has seen a reduction in the incidence of the APR and a rise of restorative proctectomy, highlighting postoperative patient function and quality of life considerations [1–5].

This chapter will explore in detail:

1. The types and methods of operations; namely, the straight colorectal or coloanal anastomosis *vs.* the colonic J-pouch anal anastomosis, the coloplasty procedure and the Baker-style colonic side-to-end anastomosis,
2. A comparison of the functional results and the morbidity of the various types of anastomosis

The main goal in the surgical management of mid- and distal rectal cancers is adequate oncologic clearance, with an effort to achieve the preservation of sphincters, sexual and urinary function. Sphincter-saving procedures for resection of both tumour and the mesorectum (partial or total) have become increasingly prevalent for the treatment of mid- and distal cancer, with a proven safety and efficacy. Total

O. Al-Bermani · P. Palamuthusingam
Department of Surgery, The Townsville Hospital, Townsville, QLDAustralia

Y. Hong Ho (✉)
Department of Surgery, School of Medicine, James Cook University, Townsville, QLD, Australia
e-mail: yikhong.ho@jcu.edu.au

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mesorectal excision (TME) involves the precise excision of the entire rectum and pararectal lymph nodes *en bloc*, within an oncologic package termed the 'mesorectal envelope'. Restoration of bowel continuity is possible in most cases, without compromise of cancer clearance. Re-anastomosis can then be performed with stapled, trans-abdominal hand-sewn or coloanal pull-through techniques. Sphincter-preserving surgery with subsequent coloanal reconstruction is preferred by most patients and results in a better quality of life than APR [6–10].

The terminology relating to the restoration of bowel continuity following rectal cancer surgery requires definition and agreement. The type of procedure is defined by the anatomical site of anastomosis rather than by the position of the cancer. The term 'high' anterior resection refers to a colorectal anastomosis performed at the level between the sacral promontory and the anterior peritoneal reflection. The level of the anastomosis is normally measured to be about 8–16 cm from the anal verge in this circumstance, depending upon the patient's body habitus. The term "low" anterior resection refers to a colorectal anastomosis performed distal to the anterior peritoneal reflection and proximal to the anorectal junction. This is normally measured to be about 5–8 cm above the anal verge, again depending upon the patient's body habitus. The term "ultra-low" or "extended" anterior resection refers to a colorectal or more usually, a coloanal anastomosis at the level of the anorectal junction. This is the type of anastomosis that is performed following total mesorectal excision with incision of Waldeyer's rectosacral fascia posterior to the rectum. The latter technical step allows the rectum to be mobilized both anteriorly and proximally from the pelvis, permitting transection of the rectum safely at the anorectal junction [11, 12]. The level of this anastomosis is normally measured to be about 3–5 cm from the anal verge. The term "intersphincteric dissection" (discussed in more detail in Chap. 13) refers to excision of a very distal rectal cancer with clear oncological resection margins by including an *en bloc* excision of the internal anal sphincter (IAS) and anal mucosa down to the level of the dentate (pectinate) line. The anastomosis is usually performed transanally as a pull-through procedure with a hand-sewn anastomotic technique joining the colon to the distal anus [11].

Anastomotic Methods

Following successful resection of the rectal cancer with total mesorectal excision, bowel continuity can be restored using various techniques.

Stapled Anastomosis

The most common method of performing the coloanal/distal rectal anastomosis is with the use of a circular intraluminal stapling instrument introduced transanally. Over the years, modifications have substantially reduced the technical difficulties attached to this type of restoration along with the risk of leak. Several randomised

studies have confirmed the validity of the stapler, examining a reduction in attendant sphincter injury, improvements in operative time and reductions in the risk of abdominal contamination [11, 13].

The transected anorectal junction tends to retract towards the pelvic floor making it technically challenging to perform a double-stapled anastomosis, which involves a hand-sewn purse-string suture to the transected rectal stump. A hypertrophied bladder, commonly found in elderly male patients with bladder outlet obstruction problems such as benign prostatic hyperplasia (BPH) can further hamper exposure. As a consequence, the Griffin-style double cross-stapled technique is the most commonly employed method particularly in the Western world designed to obviate this technical difficulty in the lower restorative case [14].

This double cross-stapled method consists of stapling and transecting the anorectal junction distal to the cancer with a transverse stapler [15] and then subsequently, the spike of a transanally introduced intraluminal stapling device is passed through the middle of the staple line into the rectal stump. The anvil of the stapling instrument is secured around the proximal cut edge of the colon with a purse-string suture and then the anvil is re-approximated to the spike, followed by a closing and firing of the stapling instrument in order to achieve the anastomosis. Prior to the introduction of any devices via the rectum, it is prudent to irrigate the transacted rectal stump with a tumoricidal agent so as to reduce the risks of cancer recurrence/implantation from exfoliated tumour cells.

A method of enabling the intraluminal circular stapling device to be introduced via the abdomen, rather than from the anus is achievable by performing a hand-sewn purse-string suture to the anorectal stump. This is discussed in more detail below in the section on "Methods of Preservation of Anal Sphincter Function".

Pull-Through Hand-Sewn Coloanal Anastomosis

The classical method of hand suturing with 'parachuting' stitches is seldom used nowadays after the introduction of stapled techniques to overcome the technical difficulties in manipulating tissue deep within the pelvis. Nonetheless, it is important that the surgeon who performs rectal surgery has the skills to construct a hand-sewn anastomosis on rare occasions when the stapling devices fail.

Stapled Instrument Malfunctioning

In this circumstance, most commonly following stapled instrument malfunction, it is not possible to re-do the double cross-stapled anastomosis, especially when the original rectal transection has been very distal. A very distal anastomosis can usually be accessed more easily for suture repair from the anus. Salvage in this circumstance of stapler malfunction include the 'pull-through hand-sewn coloanal

anastomosis', or alternatively, the transanal route can be used to insert a purse-string for a repeated stapled anastomosis where the defect is major. An appropriate defunctioning stoma would be essential in this setting.

Defunctioning Stoma

A distal colorectal/anal anastomosis at the level of the anorectal junction has a much higher risk of anastomotic dehiscence than a more proximal colorectal anastomosis [11]. Despite those anastomotic problems being subclinical most of the time, there is ample evidence to show that a defunctioning stoma reduces the complications and consequences of an anastomotic leak even in routine circumstances without necessarily reducing the incidence of the leak [16]. A defunctioning loop ileostomy has become the preferred technique by most surgeons in the West being technically easier to fashion and close, with less risk of damaging the marginal vessels than a colostomy. Colostomy is another option, preferable where the bowel preparation has been inadequate because residual faeces distal to a defunctioning stoma will continue to contaminate the anastomosis and hence will not reduce the complications of an anastomotic leak. For the same reasons, a colostomy would be preferable when the anastomosis is compromised or in places where hot weather would cause excessive dehydration from an ileostomy. A contrast study to confirm the anastomosis is intact is performed prior to reversal of a defunctioning and is traditionally done 12 weeks post- initial resection and stoma formation when the intraperitoneal adhesions would be more easily managed.

Types of Operations

Four types of operations are typically performed:

- The 'straight' colorectal or coloanal anastomosis (SCA)
- The colonic J-pouch anal anastomosis (CJP),
- The coloplasty anastomosis (CP) and
- The colonic side-to-end anastomosis (STE).

An ideal technique will combine 'good' function and minimal morbidity and our emphasis is specifically on these important aspects.

Straight Anastomosis

A straight anastomosis results from a direct end-to-end anastomosis of the colon to the anorectum as shown in Fig. 15.1. After segmental bowel resection (including right hemicolectomy, left hemicolectomy and anterior resection) for colorectal cancer, most patients (58%–78%) have a satisfactory 1–2 bowel movements per day

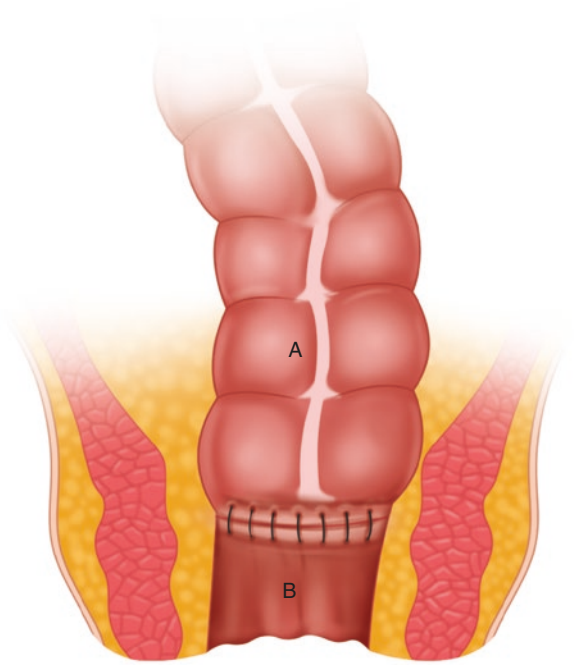

Fig. 15.1 Straight coloanal anastomosis with the colon (**a**) anastomosed directly to the anorectum (**b**)

[17]. However after low anterior resection, up to one-third of patients have 3 or more bowel movements per day. Some patients can be troubled with up to 14 stools daily [18, 19]. Other patients may have defecatory problems after anterior resection which includes excessive stool frequency but where the constellation of symptoms is broader and which has been labelled as the "anterior resection syndrome" (or **L**ow **A**nterior **R**esection **S**yndrome – LARS). This issue is discussed in more detail below and in a commentary to this chapter.

Bowel Function

Multiple regression analysis concerning the factors influencing postoperative bowel function have shown that stool frequency at 1 year is independently predicted by the level of the anastomosis and is less importantly linked to the rectal sensation [20].

Following an ultra-low anterior resection with a straight colorectal/anal anastomosis, studies have shown that stool frequency also depends upon the amount of rectum resected [11, 18, 21–23]. In this regard, there is an increased risk of poor bowel function when the level of the anastomosis is <4–4.5 cm from the anal verge (i.e. at approximately the anorectal junction) [17, 24].

The normally compliant rectum that has been removed is replaced with a less compliant segment of descending or sigmoid colon after an end-to-end coloanal (straight) anastomosis at the level of the anorectal junction. The replacement colon

is physiologically less suitable for storage/regulation of faeces [17]. Thus, the functional results include excessive stool frequency and possibly even frank faecal incontinence associated with this increased stool frequency. Anal sphincter injuries can also occur in up to 28% of patients following the transanal insertion of a stapling instrument [25] which is an important cause of faecal incontinence after a low anterior resection (*vide infra*).

Significant defecatory problems may also occur in about 28% of patients after low anterior resection [11] although the reasons for this are complex. This risk is similar to that following a sigmoid colectomy (~25%), but is substantially higher than the risk after more proximal bowel resections, such as following a right hemicolectomy (ranging from 4% to 15%) [17]. This data would suggest that the sigmoid colon may have a major role in expelling and evacuating stools [26], which would be consistent with the more muscular nature of this segment of large bowel. Resection causes discontinuity of the colonic musculature as well as the intrinsic nerves and hence, a disruption of coordinated colonic mass movement [27]. In addition, division of the lateral ligaments of the rectum during an ultra-low anterior resection may result in rectal denervation and lead to significant postoperative constipation [28].

CJP Anal Anastomosis

The delineation of the LARS post-anterior resection syndrome has led to a variety of designed strategies to improve postoperative bowel function. To date, most of these strategies have focused on the proximal aspect of the anastomosis [11]. Procedures include the colonic J-pouch (Fig. 15.2), the Z'Graggen coloplasty (Fig. 15.3) and the Baker-style colonic side-to-end anastomosis (Fig. 15.4); all techniques which have been developed and trialed with physiological considerations aimed at a better retention of stool content within the neorectum.

Physiology

The introduction of the CJP was aimed at maximising neo-rectal compliance and volume by constructing a double-barrelled configuration with limb sizes measuring up to 15 cm [19, 22, 23, 29–31]. Randomized controlled trials comparing this 15 cm colonic pouch technique with a direct straight colorectal/anal anastomosis have confirmed improved stool frequency [32–36]. Proctometrographic P/V measurements have shown improved rectal volumes and compliance [30, 36]. However, these advantages came at the expense of moderate to severe evacuation difficulty [36–39].

A smaller 6 cm CJP, was found to be effective in improving stool frequency and was associated with significantly less rectal evacuation problems [40, 41]. These results have since been confirmed by studies performed in other centres, [32, 42] and also by a randomized controlled trial from Toulouse by Lazorthes et al. compar-

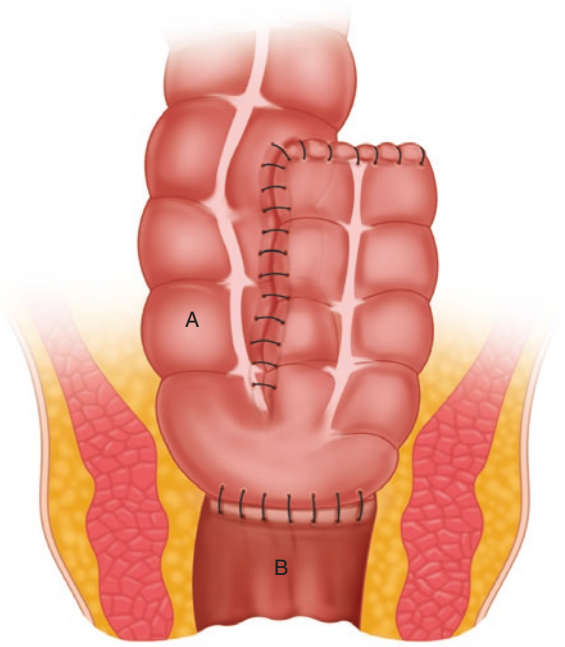

Fig. 15.2 Colonic J-pouch-anal anastomosis with a constructed colonic pouch (**a**) anastomosed to the anorectum (**b**)

ing 6 cm with 9 cm CJ pouches [35]. An interesting finding in this regard is that although there is improved function with a CJP, no differences are found in the rectal physiology (volume of initial sensation, maximum tolerable volume and compliance) measured at 1-year between a small CJP and a straight coloanal anastomosis [43]. In this randomized controlled trial, the CJP patients had less frequent stools (4.6 *vs.* 7.1 daily; $P < 0.05$), less stool clustering (35% *vs* 63.2%; $P < 0.05$) and less soiling (85% *vs* 35.3%; $P < 0.05$).

Continuous ambulatory manometry has the advantage of monitoring pressure changes in the anus and rectum over prolonged periods and in a more physiologically normal environment when compared with stationary anorectal manometric techniques. Patients with the smaller J-pouch were found to have a better tolerance to higher rectal pressures without increased stool frequencies, when compared with straight anastomosis patients in our randomized prospective trial [43]. The ambulatory anorectal pressure gradient, which has been described previously to be related to bowel frequency, was also better preserved in the CJP group [43–45].

A stool transit scintigraphy study designed by Ho et al. showed that more technetium ^{99m}Tc tin-colloid was distributed into the liquid colonic contents in the distal descending colon at 24 h in 6 cm CJP patients than in those with straight coloanal anastomosis [46]. This may be related to a "stacking up" effect from factors such as a reversed peristalsis within the CJP accounting for less frequent stools. Solid stool retention (assessed by 131I microcapsules) was also not different between CJP and straight coloanal anastomosis patients, which may explain the rarity of severe evacuation problems patients with smaller 6 cm CJP [11, 46].

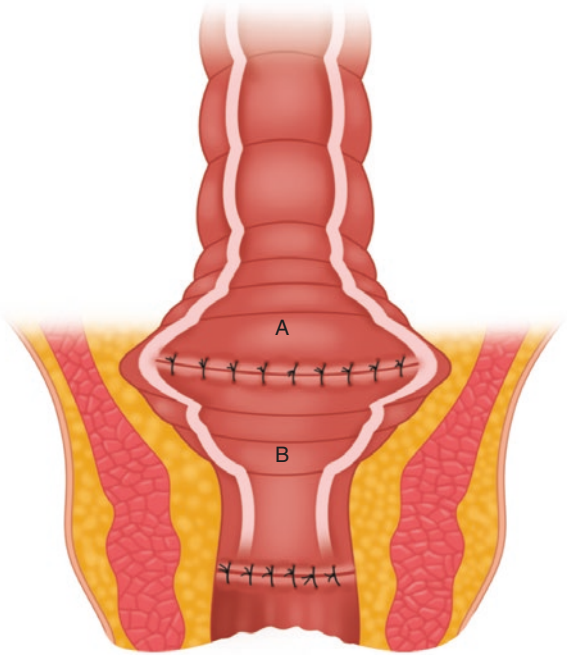

Fig. 15.3 Coloplasty anastomosis with coloplasty in the colon (**a**) anastomosed to the anorectum (**b**)

The barostat is a computerized pump that inflates a rectal balloon at controlled and reproducible rates of pressures and volumes, providing a more accurate technique for assessing rectal physiology. The only study using barostat measurements on the CJP to date showed that there were no differences at 6 months between 6 cm CJP and straight coloanal anastomosis patients [47]. At 2 years, there was a trend for improved rectal sensation and maximum tolerable volume in both types of patients. The phasic program assesses afferent sympathetic nerve function and hence these findings may be related to a specific neural recovery of function. Significant improvements in rectal compliance in straight coloanal anastomosis patients at 2 years had previously been documented in a cohort study, using traditional proctometrographic techniques [34].

Enlargement of the CJP size has been measured radiologically over a 2 year period [48]. All of these changes may be responsible for the long-term adaptation evident in patients following straight and CJP anastomoses. It is recognized that this data must be interpreted with caution since some patients in different studies would have received radiation therapy; an effect likely to impact neorectal compliance [49].

Construction of 6 cm CJP

Mobilization of the splenic flexure allows the descending colon to be used for the construction of the J-pouch. Very often this is necessitated by the sigmoid colon being badly affected by diverticulosis. Using a diseased sigmoid colon

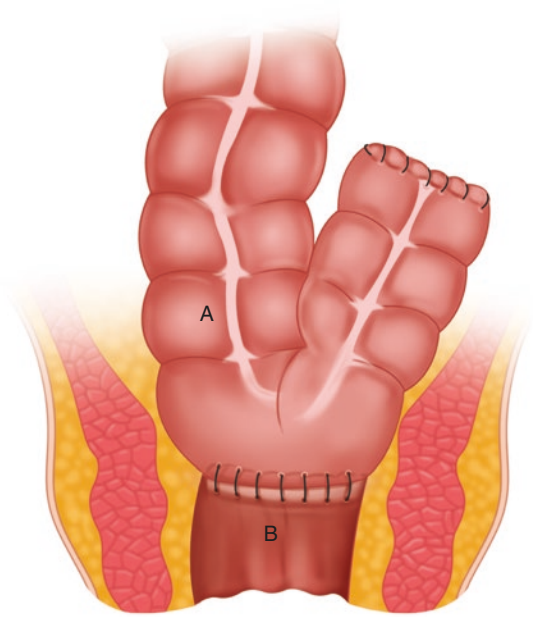

Fig. 15.4 Side-to-end anastomosis with the side of the colon (**a**) anastomosed to the end of the anorectum (**b**)

might compromise the pouch function and the anastomosis integrity. The sigmoid has been tested as an alternative to the descending colon when it is healthy and of adequate length [50]. There were no significant differences in stool frequency, incontinence, urgency, use of pads, need for anti-diarrhoeal drugs, sensation of incomplete evacuation and anorectal physiologic results at 1-year follow-up between the sigmoid and the descending colon used for CJP reconstruction. However, the descending colon has the advantage of being less muscular and more distensible than the sigmoid colon, which might account for any improvement in reported mid-term functional results [47]. Studies have shown that at 2-years of follow-up, the descending colon adapts better than the sigmoid [47].

Bowel Function

A few studies have assessed the functional and physiological outcome of the CJP and found it to be superior to the SCA, at least for the first year after surgery. Patients with a small 6 cm CJP-anal anastomosis have a median of 3 bowel movements a day compared with a median of 6 per day for patients with straight anastomoses, at 1 year after surgery [40, 41].

At 2 years of follow-up, patients with a 6 cm CJP and those with straight coloanal anastomoses have similar bowel frequency at about 1 bowel movement a day [47]. Urgency to defecate is significantly less troubling in CJP patients, however, there is a frequent sensation of incomplete neorectal evacuation which is

more common after a small CJP-anal anastomosis, although most of these patients do not require suppositories, laxatives or enemas in order to evacuate. In this respect, Lazorthes et al. [44] showed a functional superiority of CJP over SCA for up to 24 months in a randomized controlled trial with long-term follow-up. They also reported no functional improvement in their straight coloanal anastomosis patients at 2 years which may relate to their use of the sigmoid colon for their coloanal anastomoses. As the sigmoid colon is less distensible, it is less likely to adapt successfully in the long-term as a storage reservoir for faeces. This would account for the lack of difference in bowel function between colonic pouch and straight anastomosis patients, reported in cohort studies [34, 51]. Another French study by Dehni et al. [52] supported this trend of CJP superiority even up to 60 months of follow- up. This functional superiority, however, disappears beyond 2 years in a report from the Cleveland Clinic, Florida [34] and in the meta-analysis by Heriot et al., [53] there was a significant reduction in the frequency of defecation per day by 1.88, 1.35 and 0.74 motions at 6 months, 1 year, and ≥2 years, respectively in the CJP group when compared with the SCA group. Faecal urgency was also less common in the CJP group than the SCA group. Within 6 months of the procedure, 21% (44/210) with CJP had faecal urgency compared with 51.4% (126/245) in the SCA group and this difference remains statistically significant at 1 year after surgery (8.7% vs 30.3%; $P < 0.001$). By contrast, at ≥2 years, the difference in faecal urgency between these 2 groups loses its statistical significance ($P > 0.250$).

Bowel continence has been reported by some to be better in CJP patients than in those with an SCA [20, 32–34]. However, the differences are often minor and more subtle including less of a likelihood in soiling during the passing flatus [47]. At 2 years, studies to date have confirmed no differences in continence with either anastomotic type [34, 47, 54, 55]. At this stage, unless there is excessive stool frequency, it is likely that significant faecal incontinence is related more to anal sphincter injuries than to neorectal reservoir function [11].

Bowel evacuation is improved at 2 years in SCA patients, but major evacuation problems remain minimal with CJP patients [47]. Overall, 10–30% of patients with a CJP may be afflicted with evacuation problems, including constipation and fragmentation that requires laxatives, enemas and suppositories [37, 56]. A smaller pouch usually of 5–6 cm in length can be used to reduce this problem [40, 43]. A randomized controlled trial comparing the function of 6 and 9 cm CJP constructs at 2 years showed that fewer 6 cm pouch patients required laxatives and enemas for severe constipation [35]. Stool fragmentation/clustering has been defined as multiple evacuations over a 1–2 h period associated with a persistent sensation of rectal fullness. With this definition, more patients with straight anastomosis had persistent long-term stool fragmentation [51, 52]. As this phenomenon has not been confirmed in the only other large randomized controlled trial to date, these findings may well be related to cultural and dietary factors [47]. The results to date suggest that the small 6–7 cm CJP-anal/rectal anastomosis is the procedure of choice because of early improved bowel function and less risk of anastomotic complications [11].

Morbidity and Mortality

The CJP appears to be associated with a lower rate of anastomotic leak when compared with the SCA [13]. In a randomized controlled trial by Hallböok et al., [33] the anastomotic leak rates were 15% in the SCA group (n = 52) but only 2% in the CJP group (n = 45). In a meta-analysis of 7 RCTs, [57] the CJP patients (n = 139) showed a slightly lower risk of anastomotic leak when compared with the SCA cases (n = 147) (relative risk: 0.36; 95% CI: 0.12–1.08). This may be due to a better preservation of the microcirculation at the apex of the pouch in the CJP construction when compared with the bowel end in a SCA construct [13].

A meta-analysis of 35 studies involving 1050 CJP and 1066 SCA patients by Heriot et al. [53] showed no significant difference in any of the postoperative complications between the CJP and SCA groups; namely: Anastomotic leak 9.2% *vs.* 13.8% (Odds Ratio, 0.71; 95% CI: 0.48–1.03), Anastomotic stricture 7.1% *vs.* 6.7%, Rectovaginal fistula 2.3% *vs.* 2.8%, Wound infection 7.8% *vs.* 5.0% and Postoperative mortality 1.8% *vs.* 3.1%. There was also no difference in the operating time, the length of hospital stay, the incidence of nocturnal seepage and in anal manometric resting or squeeze pressures.

The lack of statistically significant difference between the 2 methods in terms of anastomotic leak may be a result of insufficient data concerning the use of chemoradiation and variation in the utilization of a defunctioning loop stoma across various studies as these have not been widely and consistently reported by many authors. Chemoradiation may increase the leak rate, while defunctioning loop stomas may decrease the "true clinically detected" leak rate by allowing small leaks to heal without any clinical signs and symptoms [57]. At the end of the day, not all patients are candidates for the CJP procedure where a narrow pelvis, a long narrow anal canal, the presenbce of bulky sphincters, and an inhospitable patient habitus can render a CJP technically challenging or sometimes impossible [57].

Coloplasty (CP)

In a sense, the concept of coloplasty is similar to that of either a pyloroplasty or a stricturoplasty, with initial performance in pigs [50, 53, 55, 58] prior to testing in human patients [59, 60]. As described earlier, a CP is an option when the pelvis is too narrow to permit a bulky CJP-anal anastomosis to be performed where it is designed to specifically 'interrupt antegrade colonic peristalsis' [54]. In order to construct a CP, a 7 cm longitudinal incision is made between the taenia along the anti-mesenteric side of the descending colon, starting 4 cm above the distal cut end. The incision is closed transversely with a continuous single layer of seromuscular absorbable sutures. The CP 'pouch' is then anastomosed to the stapled anorectal stump by a double cross stapling technique with the CP facing anteriorly as shown in the Fig. 15.3. In the event that there is any postoperative separation of the

anastomosis and peri-anastomotic sepsis, this can be drained through the midline posteriorly if the anastomosis is so orientated so that there is no risk of devascularizing the anastomosis.

Physiology

Anorectal manometric findings have not shown any significant differences in the function of small CJP and CP patients [54]. Colonic pouch reservoir function, as measured by the rectal volume of initial sensation, maximum tolerable volume and compliance, is for example not different between the groups [60]. Although surgical construction of a CP provides a 40% increase in neorectal volume [58], it is more than likely that in the clinical situation motility factors such as disruption of colonic propulsion as a result of placement of the CP on its anti-mesenteric surface may be more important [59].

Bowel Function

The differences between the early functional results of the small CJP and CP techniques are subtle. In this respect, Ho et al. [54] found that the bowel function at 4 months was different between CJP and CP cases. In this setting, the patient with a CP was able to defer bowel movement somewhat better and reported less nocturnal leakage. By contrast, the CJP patients had significantly less stool fragmentation requiring a return to the toilet at least once within 15 min of the primary evacuation. Each of these parameters equalized over time and were not significantly different between the 2 groups by 1 year of follow-up. Furthermore, there were no significant differences concerning other evacuatory and ancillary parameters including continence, the quality of life, anorectal manometry and endoanal ultrasound findings between the 2 studied groups. Overall, CP patients tend to have a significantly better stool deferment time with less nocturnal liquid stool leakage. Pimentel et al. [61] and Fürst et al. [62] have both supported these findings in their randomized controlled trials. They also reported no statistically significant difference between CJP and CP in terms of their bowel function parameters which included frequency, urgency, fragmentation, incontinence, nocturnal leaks and anorectal manometry. Pimentel et al. [61] in a study from Portugal found that at 1 year of follow-up, 2 (14.3%) of the CJP patients required enemas in order to evacuate their pouch and to provoke defecation, with this symptom not found amongst the CP patients. The patient perceptions, as measured by the Faecal Incontinence Quality of Life (FIQL) scale, also showed no differences between the small CJP and the CP techniques. Similarly, Fürst et al. [62] in a study from Regensburg Germany could only demonstrate a subtle increased in neorectal sensitivity in the coloplasty group unaccompanied by any clinical benefit in stool frequency.

Fazio et al. compared their CJP and CP patients in a randomized trial [59]. Overall, the CJP patients had statistically fewer bowel movements per day at 4, 12 and 24 months of follow-up with less stool clustering (40% of J pouch patients *vs.* 63% of coloplasty patients, respectively; $P < 0.03$ at 24 months). The CJP patients reported less faecal incontinence with lower FISI scores at 4 months (39.5 *vs.* 51, respectively; $P = 0.001$) and at 24 months (31.1 *vs.* 36.8, respectively; $P = 0.04$).

Morbidity and Mortality

Currently, there are 3 available RCTs [54, 59, 61] involving 158 patients which compare the results of CJP and CP cases. Ho et al. [54] examined 44 CJP and 44 CP cases and found that a CP resulted in significantly higher anastomotic leak rates when compared with a CJP (15.9% *vs.* 0% respectively; $P < 0.01$). The CP resulted in a clinical leak rate of 7% and a radiological leak rate of 9%. Leaks were noted to occur at the anterior part of the anastomosis generally below the site of CP formation. None of the patients had received postoperative radiotherapy or chemotherapy. It is proposed that the CP has an end-to-end configuration and that the blood supply can be being compromised directly because of this arrangement. This increased rate of anastomotic leakage with the CP is supported by the RCT conducted by Pimentel et al., [61] where the leak rate for CP was 13.2% compared with 6.6% for a CJP, although this did not reach statistical significance due to small patient numbers in both arms.

By contrast, the RCT conducted by Fürst et al. [62] did not report data on anastomotic leakage although this aside, there was no significant difference in other postoperative morbidities, such as pouch-vaginal fistula, anastomotic stricture or wound infection and the mortality between the 2 groups in all 3 RCTs was no different for the two main operations [13].

It is important to note that construction of a CJP may not always be possible due to a narrow male pelvis, a short fat mesocolon, or because of extensive colonic adipose tissue. Concerning this matter, Fürst et al. [62] reported that a CJP was feasible only in 75% (15/20) of randomized patients, whereas a CP could be successfully performed in all allocated patients. Fazio et al. [59] compared their straight colorectal anastomoses with their CP reconstructions. There are some demographic biases in this paper since comparison was made exclusively in patients with low rectal cancers who were ineligible for a colonic J pouch. Overall, these patients had a higher BMI than patients who were eligible for a J pouch (30.5 *vs.* 26.9, respectively; $P < 0.001$) and likely had a more challenging anatomy than the typical patient with a low rectal cancer (89% males *vs.* 64%, respectively). No differences were, however, detected in most of the measures of anorectal function at 4, 12 and 24 months of follow-up. Specifically, continence was slightly worse at 4 months in the CP group with the CP patients experiencing anastomotic separation in 8.5% of J-pouch ineligible cases (versus 4.6% for J-pouch eligible patients) and anastomotic stricture in 12.8% of J-pouch ineligible patients (compared with 3.8% in J-pouch eligible patients).

Currently, because of a higher risk of anastomotic complications, the CP cannot be recommended except in special circumstances when a bulky J-pouch cannot readily be brought through a narrow pelvis for anastomosis to the anorectal junction. In these cases, a defunctioning stoma is advisable. There is generally, however, a paucity of literature comparing the straight anastomosis with the CP procedure. A large, multi-centre randomized controlled trial with adequate power to determine if there is an increased risk of anastomotic leakage with the CP is required before a transverse CP can be recommended as a viable alternative to the CJP or to a straight anastomosis.

Side-To-End Anastomosis

The side-to-end (STE) anastomosis as shown in Fig. 15.4 was first described by J.W. Baker in 1950 [63] and as an operation, its use has been revisited recently as another option designed to improve postoperative bowel function. There are 2 variations of the procedure; namely:

1. The anastomosis is performed by introduction of the intraluminal stapler from the anus or
2. The anastomosis is conducted entirely from via abdominal route.

Methods of Preservation of Anal Sphincter Function

Some risk to the anal sphincter can be anticipated with low anterior resection [43, 64, 65] primarily related to injury to the internal anal sphincter (IAS) from the transanal introduction of the stapling device. It is reported that faecal continence may be compromised in 13%–80% of patients [10, 18, 19]. Horgan et al. [66] monitored the anal pressures of patients on the operating table undergoing anterior resections reporting that anal pressures were maintained at the time of the division of the inferior mesenteric artery, during full mobilization of the rectum and the mesorectum and also during the anal transection. Pressures decreased significantly only after the transanal introduction of the intraluminal circular stapler, suggesting a direct sphincteric instrumental injury.

Molloy et al. [67] found that anal resting pressures in dogs were significantly lower following the transanal introduction of an intraluminal circular stapler comparing these cases to hand-sewn colorectal anastomoses. There was a significant diminution in anal pressures after both types of anastomoses suggesting that nerve injury during rectal mobilization may also be a contributing factor. A randomized controlled trial showed that direct injuries to the IAS could be avoided with the biofragmentable anastomotic ring (where the anastomosis was performed entirely intra-abdominally) for a high anterior resection [68].

Bowel Function

Machado et al. [69] performed a randomized controlled trial comparing a colonic pouch with the STE anastomosis, showed that the STE technique was functionally comparable to the 8 cm CJP when the anastomosis was performed with transanal introduction of the intraluminal stapler. The only difference noted in this Swedish study was a better neorectal evacuation in <15 min in the CJP group at 6 months. Function again seems to be related to timing. By 6 months, Huber et al. [70] reported a median daily stool frequency in CJP and STE groups at 2.3 (0.5–3) and 3.1 (1–5), respectively. This was the only study to show a statistically significant difference in stool frequency in the short-term. The CJP group was reported to have better stool frequency at 3 months, but the functional results equalized in both groups by 6 months. Equally, Jiang et al. [71] reported a mean daily stool frequency of CJP and STE of 2.3 (0.2) *vs*. 1.9 (0.2) at 1 year and 1.9 (0.2) *vs*. 2 (0.3) at 2 years. Machado et al. [72] reported a median daily stool frequency of CJP and STE as 3.1 (1.9–3.8) *vs.* 3.0 (2–4.9) at 1-year of follow-up and 2.6 (1.4–3.5) *vs*. 2.4 (1.4–3.9) by 2 years of follow-up. At 1 and 2 years, both studies reported no significant differences in stool frequency between the CJP and STE groups [13]. In general, there is a trend towards a decreased stool frequency in both groups in the long-term and this demonstrates the prevailing views concerning our understanding of the adaptive changes in the neorectum with time [13]. There was no significant difference reported in urgency at 6 months for all 3 studies with Machado et al. [72] actually demonstrating a trend toward less urgency in the CJP group by 2 years.

The 3 studies used a variety of methods for intraluminal stapler introduction; namely: a totally trans-abdominal technique for both groups in the study by Jiang et al., [71] a totally transanal stapling for both groups in the study by Machado et al. [72] and a transanal approach for CJP construction with a transabdominal approach for the STE procedures in the study by Huber et al. [70]. Regarding faecal incontinence, there was no difference at 6 months between all of the groups despite the study heterogeneity.

The STE anastomosis should theoretically obviate some of the evacuation difficulties encountered with the CJP technique even though the RCTs have failed to demonstrate any advantage in up to 2 years of follow-up [13]. The data here are actually mixed with Huber et al. [70] showing poorer evacuation in the CJP group than in the STE group in the early (3 months) postoperative period. The reverse findings at 6 months were reported by Machado et al. [72]. Overall, there were no differences in evacuation difficulties reported between the groups at all other times. A failure to demonstrate any difference may be due to the smaller (5- to 8-cm) pouches constructed in these studies.

Neorectal volumetry was significantly different between the groups in the study by Huber et al. [70] and by Machado et al. [72]. The median threshold and the maximum tolerated volumes were significantly lower in the CJP cases compared with the STE patients at 6 months [70] (243; 210–265 and 53; 42–63 mL compared with 296; 275–315 and 296; 275–315 mL, respectively). In the Machado study [72] by 2 years the

maximum (median) neorectal volume was greater in the CJP patients compared with the STE group (178;140–226 *vs*. 126; 104–150 mL, respectively: $P < 0.01$). It is interesting to note that the 2 studies employed 6- and 8-cm J-pouches, respectively, compared with an STE procedure where there was a regulated 3–4-cm "efferent" limb. The larger neorectal volumes of the CJP reported by Huber et al. [70] did seem to translate into significantly less bowel frequency over the short-term, but this was not replicated in the larger Machado study, [72] providing further evidence that an increased neo-rectal capacity does not readily translate into functional improvement. The reason for the STE procedure having equivalent bowel function when compared with a CJP (even over a 6- to 12-month period), may be due to a reverse or anti-peristalsis which is generated in the side limb of the STE and the short limb of the CJP.

Overall, safety and postoperative functional outcomes between CJP and STE are comparable. All 3 studies concluded that an STE procedure can be an acceptable alternative for ease of construction and be specifically useful in times of technical need (such as where an insufficient colonic length or a narrow pelvis are encountered). Technical ease needs to translate to faster operating times and this is only evident in the study reported by Huber et al. [70]. Performing an anastomosis in a narrow pelvis with a flopping side limb as compared with a congruently formed pouch may be equally cumbersome, if not more so. The optimal length of the STE efferent limb is also uncertain and it would appear that until more convincing evidence is presented, the CJP procedure should remain the standard operation in those cases where short-term functioning is paramount.

Morbidity and Mortality

A unique complication of the STE anastomosis technique is bowel obstruction secondary to an inadvertent inclusion of the side-wall of the opposite limb into the anastomosis. Unlike the CJP, the STE anastomosis has a narrow lumen which makes inclusion of the side-wall a potential risk [11]. Nonetheless, as both the CJP and the STE anastomoses are essentially side-to-end in style, the vascularity and the related complications would be expected to be similar. This has proven to be the case in reported studies and case reports. A Cochrane meta-analysis review showed an increased risk of anastomotic leak with the CJP, however, this did not reach statistical significance [7]. Total postoperative complications ranged from 10.3%–28% for CJP and from 10.7%–22% for STE in the pooled analysis, however, there was no significant difference between the postoperative complication rates between the two techniques [7, 13]. In summary, there is no significant demonstrable difference in urgency, faecal incontinence or incomplete evacuation between CJP and STE techniques. The STE technique appears to result in a similar bowel function to the CJP method with similar postoperative complications and complication rates. Further study is necessary in order to confirm that functional outcomes are similar and this may enable the STE anastomotic technique to supplant the other options particularly because of its ease of construction even when there is challenging anatomy.

Management of 'Anterior Resection' Syndrome

The primary postoperative neorectal anastomosis is associated with a specific defecation disorder; the **L**ow **A**nterior **R**esection **S**yndrome of LARS. The symptoms of LARS include a mix of increased bowel frequency, urgency and incontinence. The most striking symptom of LARS is the feeling of not adequately emptying (incomplete defecation) despite the fact that the bowel is frequently empty. Several types of pouch surgeries have been designed in an effort to solve this problem.

Conservative Management

Traditionally, the management of poor bowel function has been expectant having excluded other causes particularly including tumour recurrence and pelvic sepsis. It is now known that the colonic adaptation can take up to 18 months following an ultra-low anterior resection with total mesorectal excision [47]. The patient is advised to take adequate soluble fibre in the diet, (pasta, rice and bananas) and to avoid foods which clearly aggravate bowel dysfunction. There are however, no randomized trials assessing these effects. Those with increased stool frequency may be prescribed diphenoxylate, codeine and/or bile salt-binding agents to help control the symptoms. Patients with rectal evacuation problems may be prescribed regular laxatives and enemas. On rare occasions, patients fail to respond to basic conservative treatments and have persistent debilitating bowel function lasting beyond 18 months. Under these circumstances, anorectal biofeedback therapy and/or postanal sphincter repair may need to be considered. A stoma would be only needed in very exceptional circumstances [73, 74].

Anorectal Biofeedback and Sacral Nerve Modulation (SNM)

Biofeedback has been shown to be effective in treating certain types of faecal incontinence [75]. Biofeedback has been reported to be successful in managing patients who have stool frequency and/or incontinence problems specifically after anterior resection [76]. In our study at a mean follow-up of 10.6 months, there was a 90% success rate without clinical regression decreasing stool frequency (8.7 SEM 2.1 before *vs.* 4.6 SEM 1.2 afterwards; $P < 0.05$) as well as incontinence episodes (2.7 SEM 0.9 before *vs.* 0.4 SEM 0.2 afterwards; $P < 0.05$). Anorectal physiologic testing performed before and after biofeedback, however, will show minimal increase in anal pressures. It is possible that biofeedback works in a more complex and coordinating manner by improving the anal sphincteric coordination, rectal sensation, rectal liquid retention and/or anal canal sensation [11]. Although the patient-biofeedback therapist relationship is probably vital in ensuring treatment success,

none of the patients in our small study had any formal psychiatric counselling [77]. Biofeedback has also been reported to be 90% successful in managing intractable constipation following low anterior resection [78]. Intractable constipation after low anterior resection is likely to result from resection of the propulsive component of the large intestine, the sigmoid colon [26]. The results of pre- and post-biofeedback anorectal physiologic testing are, however, inconclusive, suggesting that similar factors outlined previously may play an important role in bringing about the positive changes in bowel function [11].

There has been growing interest in the use of sacral nerve modulation (SNM) [79–81] for the management of anterior resection syndrome. The exact mechanisms remain to be elucidated however there are some early trials showing promise and further studies are awaited. Given the complexity of postoperative function in an eclectic group of patients (radiation effects, anal sphincter injury, postoperative pelvic sepsis, compliance and capacity problems of a neorectal reservoir; poor pouch propulsion; pudendal and autonomic neuropathy; uncoordinated anorectal gradient, etc.;) even though the mechanisms of action of SNM are unclear, it would seem a logical option because of its minimally invasive nature, safety and reported impact on quality of life [82, 83].

Postanal Sphincter Repair

Treatment options are limited for persistent intractable excessive stool frequency and incontinence after low anterior resection for rectal cancer. Fortunately, this is quite rare, but such patients treated successfully by postanal sphincter repair have been reported [84]. Endosonography supplemented by anorectal manometry, most typically shows an internal anal sphincter (IAS) disruption following transanal stapler insertion which may potentially be treated more successfully with IAS implants [85, 86]. Historically, our group has performed a postanal repair on a small number of cases showing a reduction in the mean number of stools per day (5.7 down to 1.7) [84]. Faecal incontinence requiring pads in all the patients so treated was improved to full continence in 67% of cases and to minor incontinence for flatus in 33% of patients. The continence score improved from a mean of 13.7 down to a mean of 1.3 over a median of 3.2 years of follow-up in our small study.

Laparoscopic Ultra-Low Anterior Resection

Laparoscopic colonic cancer surgery is considered at least as safe and as effective as traditional open surgery. However, data is still limited with regard to the laparoscopic management of rectal cancer. It is now technically possible to perform

the mobilization of the left colon and total mesorectal excision by a laparoscopic technique. The anorectal junction can be stapled and transected with an endoscopic linear cutter stapler. The specimen can then be extracted through a plastic drape protected 4–5 cm muscle splitting transverse incision, which can be used eventually for the temporary defunctioning stoma. A CJP or CP can be performed extracorporeally and pneumoperitoneum reconstituted so as to perform an intracorporeal end-to-end double cross stapled anastomosis, with the intraluminal stapling device introduced transanally. Further data and refinement of the technique is awaited.

At present, the small CJP-anal anastomosis is the most widely accepted method of restoring colonic anal continuity after a total mesorectal excision. A straight colorectal anastomosis is preferred where the anastomosis is more than 4–6 cm above the anal verge. In these circumstances, there is adequate residual rectum to provide the necessary rectal reservoir capacity. In this setting, however, construction of a CJP-rectal anastomosis at this proximal level may result in rectal evacuation problems. Selvindos et al. [87] have elegantly described a total laparoscopic STE coloanal anastomosis with 5 mm ports where incision used for specimen retrieval is also the site of the stoma. Where a coloanal anastomosis at the anorectal junction is considered in a heavily built patient with a narrow pelvis and inadequate proximal bowel length, a straight anastomosis with or without a CP is a preferred option. Other methods for restoring bowel continuity are best reserved for specialized circumstances such as when there is a staple gun misfire or where there are unique anatomical difficulties [60].

Impact of Neoadjuvant Radiotherapy

There is not a lot of literature addressing the functional impact of adjuvant radiotherapy and its association with bowel function following rectal resection [88, 89]. There are no randomized trials of RT use and function with studies where there has been a radiotherapeutic arm only showing broadly worse overall functional outcome. Many of the trials of SCA *vs.* CJP were conducted in the 1990s; an era when the impact of radiotherapy on reducing local recurrence after TME had not been clearly elucidated. These studies also do not take into account improvements in RT delivery to the pelvis. More recent studies comparing STE with CJP reflect a change in practice, where radiotherapy is utilized in most of the included patients. The indices of bowel function do not appear grossly worse in recent studies where RT has been more routinely employed although subgroup analysis and stratification based on RT scheduling is needed for future trials [74]. A recent study by Qin et al. [90] has shown that deterioration in reported function after anterior resection for rectal cancer is more associated with long-course RT particularly in lower third of rectum cancers and that thickening of the rectal wall as measured on pelvic MRI is a predictive factor.

Implications for Practice

After low anterior resection for rectal cancer, coloanal reconstruction with the CJP leads to better bowel function and similar rates of postoperative complications when compared with the SCA operation. This improved bowel function seems to persist for up to 2 years after gastrointestinal continuity is reestablished and thereafter functional outcomes are similar between the two procedures. Thus, the CJP should be considered the procedure of choice after proctectomy for rectal cancer. While there is limited literature comparing the transverse CP procedure with the CJP, three small randomized trials suggest that bowel function is similar in patients reconstructed with either technique [46, 61, 91]. However, there is some evidence that the transverse CP procedure results in more frequent anastomotic dehiscence. Given this consideration, currently the transverse CP procedure should only be used in the context of a clinical trial registry.

The STE anastomosis is a compelling alternative to the CJP that has similar functional outcomes in three small randomized trials so far reported. Further study is necessary before this technique can be more broadly recommended, however, in those patients whose anatomy is not amenable to a CJP reconstruction, the STE anastomotic technique is a viable alternative.

Implications for Research

Further evaluation of the transverse CP and STE anastomotic strategies are necessary to ensure their relative safety and to define their effectiveness as alternatives to the CJP. Standard definitions of frequently used bowel function outcomes should be established in order to facilitate valid comparisons of anastomotic and other bowel function interventions between studies. Standardization of LARS-related questionnaires and their validation also needs to be established [92].

Conclusion

Evidence from the current literature shows that a CJP results in superior bowel function when compared with an SCA for at least 2 years after surgery. In addition, the CP and the STE type anastomoses appear to have similar advantages but require larger studies with more long-term prospectively collated data. The surgery for rectal cancer continues to develop towards the best balance of the ultimate goals of improved local control and overall survival, the maintenance of a good quality of life, preservation of the sphincters and optimal genitourinary and sexual functioning.

Commentary: Low Anterior Resection Syndrome – What's New?

Andrew P. Zbar

Drs Bermani, Palamuthusingam and Ho eloquently discuss the problem of the Low Anterior Resection Syndrome euphemistically referred to in the colorectal literature as LARS. It is only relatively recently that special symptomatology following a low neorectal anastomosis has come to light with an improvement in the registration and follow-up of patients where upwards of 80% recognize some variant of a constellation of postoperative symptoms which include urgency, clustered defaecation, evacuatory dysfunction (and frequently difficulty) and even frank incontinence. The aetiology of LARS is mixed but includes the postoperative disruption of the rectoanal inhibitory reflex, reflecting the capacity of the neorectal reservoir but also since there are differences initially encountered with pouch-style and Baker-style anastomoses, of the propulsive mechanisms of the reservoir itself. Add to this alterations in mucosal sensitivity (particularly when a mucosectomy or a coloanal pullthrough has been performed), differential pudendal and autonomic neuropathy, alterations in the postoperative rectoanal gradient and the potential of anal sphincter distraction and injury and it can be seen that the final common pathway of LARS will incorporate an eclectic group of patients [93]. The increased propensity for LARS will reflect too the more widespread use of radiation therapy and the complexity of induction and consolidation add-on chemotherapeutic scheduling, both of which will impact the ultimate functional result.

In this morass, Laurberg and colleagues along with others aimed to validate some of this symptomatology and to equate its direct impact on patient quality of life. A symptomatic score was initially constructed using regression analysis to determine individual risk ratios, designating LARS in a binary manner as either minor or major [94]. Like the initiation of all tests it had sufficient pilot acceptance and comprehension along with test-retest reliability. Importantly, this questionnaire has been extensively validated in complex surgical environments where there are a range of colorectal restorative techniques, [95] or in minimally invasive surgery [96] as well as in those patients undergoing radiotherapy and neoadjuvant therapy [97] and as a translated instrument in different countries [98–101]. These latter techniques have required a back and forth translation and prospective utilization in post-LAR populations, showing particularly useful reliability in a range of different cultures.

The ideal type of instrument needs to assess the impact of specific post-LAR symptoms on quality of life and not act as a mere surrogate for incontinence grading. In this regard clustering appears to be a much more sensitive marker, recognizing the fact that up to 40% of postoperative patients may become toilet dependent in one way or another [102]. Of course, individual results may appear acceptable if such questions are never asked. Moreover, the duration of necessary follow-up in

the assessment of LARS is presently undefined, with an expected remodeling of stool pattern over the first 2 years but potentially with small incremental improvement from then onwards, sometimes out to many years [103].

Our patients will be substantially aided by improvements in RT technology and we will hopefully learn from some of the data which will come out of the **O**ptimising **R**adiotherapy **B**owel **I**njury **T**herapy (ORBIT) study [104]. New protocols will better define those very low risk cases where short-course RT can be avoided and at the other end of the spectrum, high-risk patients who will functionally benefit from intensity modulated RT (IMRT) régimes or consolidating therapies between CRT and surgery. Symptom-based questionnaires and their validation for those patients with ultralow rectal cancers treated successfully with organ preservation are awaited. The combined attempt by the UK and Danish LARS Study Groups to identify significant preoperative factors through a designated POLARS (**P**re**O**perative LARS) score which encodes for poor post-LAR function is commendable and their data are also eagerly anticipated [105].

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Chapter 16
Multivisceral Resection: Technical Considerations

Nabila Ansari and Michael J. Solomon

Introduction

Locally advanced rectal cancer with adherence to or invasion of adjacent organs accounts for 6–10% of all primary rectal cancers [1, 2]. The incidence of local recurrence after rectal cancer surgery is decreasing as a result of improved surgical techniques and preoperative radiotherapy. In this regard, studies from the 1970s and 1980s demonstrated failure rates as high as 25–40% [3, 4]. More recently, these rates have been reduced to 5–15% [5–7]. This group of patients with locally advanced primary and locally recurrent rectal cancer present a complex management problem with significant symptomatic consequences related to the invasion of pelvic structures.

Pelvic exenteration (PE) surgery was first reported in the literature in 1948 by Brunschwig as a palliative operation for advanced cervical cancer [8]. However, it has only been recently, in the past two decades, that PE surgery has evolved to an extent where there is now a significant number of case series reported in the literature demonstrating acceptable morbidity, mortality and quality of life indices. The alternative non-surgical treatment options for these patients include palliative chemotherapy, radiotherapy and supportive treatment. These management options carry a poor prognosis with short-term relief of symptoms and a median survival of only 10–17 months [9–11]. When disease progression occurs, it results in pain, bleeding, intestinal and urinary fistulae as well as bowel obstruction prior to death.

N. Ansari
Department of Colon & Rectal Surgery, Royal Prince Alfred Hospital, Sydney, NSW, Australia

M. J. Solomon (✉)
Royal Prince Alfred Hospital, Camperdown, NSW, Australia

RPAH Medical Center, Newton, NSW, Australia
e-mail: professor.solomon@sydney.edu.au

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With improvements in radiological assessments, surgical techniques and postoperative care, radical resection for locally advanced and locally recurrent rectal cancer has become the preferred treatment option for a select group of patients.

Recent series on PE surgery for recurrent rectal cancer have reported overall 5-year survival rates of 20–35% [12–16]. Series on PE for primary advanced rectal cancer report better overall 5-year survival rates of between 36% and 52% [17–21]. Studies also demonstrate that PE surgery can be performed successfully with minimal perioperative mortality rates of 0–1% [12–14]. It should also be noted that the extent of resection does not influence long-term survival [12, 13, 15, 22]. Postoperative morbidity however, remains a substantial burden with reported rates of up to 80% [12, 13, 18, 21–23]. Equally important, the long-term quality of life in survivors of PE for recurrent rectal cancer has been shown to be comparable to early results following primary rectal cancer resection and better than in patients who receive non-surgical palliative treatments [24–26].

Pelvic exenteration surgery is technically challenging due to the anatomical confines of the bony pelvis and loss of surgical planes from previous surgery and radiotherapy. Therefore, PE surgery is best performed in specialised units. This chapter focuses on the technical aspects of PE surgery.

R0 Resection: "The Holy Grail"

The most important aim of PE surgery is to completely resect all malignant disease in order to achieve an R0 resection margin. Most series demonstrate that R0 resection predicts greater survival and better quality of life. In one extensive pooled analysis of 1569 patients who underwent PE surgery, the average overall 5-year survival rate was 30.7%. This was even higher, at 38.2% in those patients in which a clear resection margin (R0 resection) was achieved [27].

With greater surgical experience and improved techniques, R0 resection margin rates have improved considerably. R0 resection is more achievable in locally advanced primary colorectal cancer than in recurrent tumours, with a recent series of 100 exenteration patients treated at the Royal Marsden Hospital, London demonstrating R0 resection rates of 91% in locally advanced primary colorectal cancers versus 62% in locally recurrent colorectal cancers [28]. Central (axial) and anteriorly positioned lesions are more likely to have an R0 resection than lesions in other locations, especially lateral (pelvic side-wall) tumours [29]. The largest current series of radical resection with sacrectomy for posterior tumours reports an achievable R0 resection rate of 74% in 79 patients [30]. Furthermore, PE surgery for more formidable lateral recurrence is also possible with R0 resection rates of 53% reported which was associated with 0% perioperative and 30-day mortality. Our group reported that 46% of patients were disease free with an average disease-free interval of 30 months [31].

Preoperative Assessment

All decisions regarding the management of patients considered for PE surgery should be made in a multidisciplinary setting. The multidisciplinary meeting should involve the various surgical, oncological, radiological and perioperative anaesthesiology specialties. In addition, allied health specialists including stomal therapy, rehabilitation, pain, nutrition and psycho-oncology opinion should be sought. All patients should have pelvic and any distant disease evaluated by computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) prior to consideration of surgery.

MRI is essential for determining resectability and for planning the surgical approach. MRI scan provides an assessment of the tumour and the extent of involvement of adjacent pelvic viscera, including invasion into bone, nerve, vessels and ligaments. A disadvantage of MRI is the difficulty in distinguishing between recurrent disease and post-radiotherapy or post-surgical changes [32]. In this scenario, PET or PET/CT can help to distinguish between tumour and fibrosis or inflammation [33].

PET scans are invaluable for the detection of disseminated disease and have been shown to alter the management of up to 40% of patients with advanced colorectal cancer by demonstrating distant disease that was not detected on CT imaging [34]. It should be noted, however, that the presence of peritoneal disease may be missed on both CT and PET scanning. Furthermore, PET scanning is less accurate for mucinous colorectal adenocarcinomas and can be falsely positive if there are ongoing inflammatory processes [35].

Absolute and Relative Contraindications for Pelvic Exenteration

Patients need to be relatively fit in order to withstand the physiological stress of PE surgery, ideally with an American Society of Anaethesiologists (ASA) score of 3 or less. The tumour should be localised to the pelvis without distant metastases, unless distant metastases are resectable with curative intent. As PE surgery evolves, so do the absolute and relative contraindications to surgery. This was investigated in a recent international study that assessed clinical, MRI and PET-CT factors used by surgeons to determine suitability for pelvic exenteration and demonstrated that absolute contraindications are diminishing as surgical boundaries are pushed and techniques developed [36]. Some absolute contraindications remain, however and these include poor patient performance status, multiple distant metastases and sacral involvement necessitating resection of the entire sacrum [36]. Current contentious issues revolve around the traditional anatomical limits of resection and apply to

Table 16.1 Absolute and relative contraindications for pelvic exenteration surgery

Study	Absolute contraindications	Relative contraindications
Boyle et al. [37]	Encasement of external iliac vessels	Distant metastases
	Extension of tumour through sciatic notch	Primary stage IV disease
		Extensive pelvic side-wall involvement
	Presence of lower limb oedema from lymphatic or venous obstruction	Inability to achieve R0 resection
	Poor performance status	Sacral invasion above S2/S3
Pawlik et al. [38]	Distant metastases	Ureteral obstruction
	Involvement of common or external iliac vessels	Significant medical comorbidity
		Poor performance status
	Para-aortic lymph node metastases	
	Involvement of sacrum above S1	
	Tumour extension through sciatic foramen	
	Pelvic side-wall involvement	
Ogunbiyi et al. [39]	Tumour invading above S2	Distant metastases
	Involvement of pelvic side-wall or pelvic nerves	Diffuse intra-abdominal nodal metastases
	Involvement of ureters or presence of hydronephrosis on imaging	

lateral and posterior compartment tumours in particular, where there may be involvement of any bone other than S2 down and major vascular or lumbosacral, sciatic or femoral nerve involvement. Multiple publications have defined absolute and relative contraindications to PE surgery (Table 16.1).

Lateral pelvic side-wall involvement is no longer an absolute contraindication with acceptable R0 resection rates demonstrated with extended lateral resection [31]. Extended lateral resections can involve lateral pelvic bone and ligament resection, which enables removal of cancer that extends to and through the greater sciatic foramen. Lateral nerve involvement is also not an absolute contraindication as adequate lower limb motor function can be retained even with removal of the lumbosacral (L4/5) and S1 nerve roots. Similarly, resection in the presence of external iliac vessel encasement is not absolutely contraindicated as the vessel can be resected to achieve an R0 margin and then blood supply restored after vascular reconstruction [40]. It is accepted that within this group, R0 resection margins are less likely but over the medium-term vascular graft patency is high with a median overall and disease-free survival of 24 and 26 months respectively. Likewise, ureteric involvement is also no longer an absolute contraindication to PE. Unilateral nephrectomy, ureterectomy and reimplantation or radical cystectomy and construction of an ileal conduit are all surgical options depending upon the extent and level of ureteric invasion [41].

Metastatic disease no longer precludes patients from PE. There is a small group of highly select patients with limited and resectable metastatic disease such as unilateral liver metastases or solitary pulmonary metastases who may still benefit from PE [42]. PE in these patients should however, be performed only after much deliberation and debate.

Very rarely, PE can be performed as a palliative procedure such as in cases with difficult to manage malignant masses where there is small and large bowel to vesical, vaginal or cutaneous fistulae or in some specific cases of unmanageable malignant cutaneous and vaginal wounds. Palliative PE can also be considered in the setting of intractable sciatic nerve or pelvic soft tissue pain. For all patients, quality of life and patient choice are significant considerations before embarking upon such radical surgery. It should be noted that in general, palliative pelvic exenteration carries the highest morbidity and the lowest quality of life.

Anatomical Considerations

Patients presenting with locally far advanced and locally recurrent rectal cancer are a complex and heterogeneous group with respect to involved pelvic structures. The type of operation performed is dictated by the site and size of tumour and the number of other adjacent organs that are involved. The crucial aim of surgery is to achieve a clear resection margin (R0 resection) which may necessitate the *en bloc* removal of other organs including the rectum, bladder, prostate, uterus and fallopian tubes, vagina, pelvic nerves and vessels, muscle, ligaments and bony components of the pelvis such as the sacrum.

In order to better understand the operative approaches, the pelvis can effectively be divided into four main compartments with considerable overlapping boundaries (Fig. 16.1).

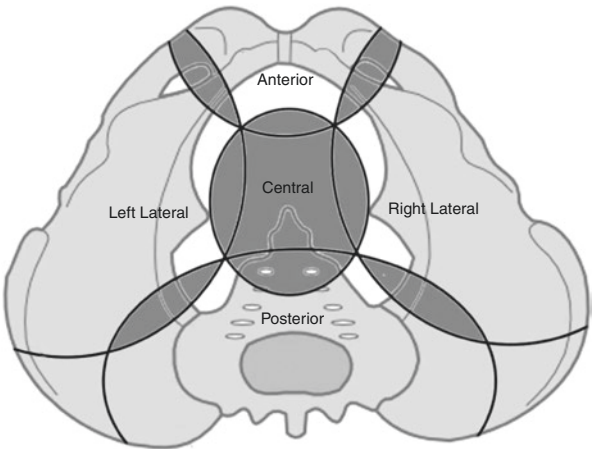

Fig. 16.1 Anatomical compartments of the pelvis

1. ***Anterior compartment:*** consists of the bladder, prostate, seminal vesicles, vas deferens, urethra, urogenital diaphragm, dorsal vein complex, obturator internus and externus muscle, anterior half of the vagina, anterior pelvic floor muscles (pubococcygeus and puborectalis part of levator ani), and pelvic bone (pubic symphysis, superior and inferior pubic rami).
2. ***Central compartment:*** consists of the posterior half of the vagina, uterus, ovaries, fallopian tubes, broad ligament, round ligament of the uterus, rectum, pelvic floor muscle (iliococcygeus part of levator ani), lower sacrum (S4 and below) and coccyx.
3. ***Posterior compartment:*** consists of the rectum, pelvic floor muscle (coccygeus), internal iliac vessel branches and tributaries, piriformis muscle, sacral nerves S1–S4, pelvic bone (sacrum and coccyx), anterior sacrococcygeal ligament, medial sacrotuberous and sacrospinous ligaments.
4. ***Lateral compartment:*** consists of pelvic side-wall structures, ureter, internal iliac vessels, external iliac vessels, piriformis and obturator internus muscle around the ischial spine, coccygeus muscle, lateral sacrospinous ligaments attached to ischium, ischial tuberosity and spine, lumbosacral trunk and sciatic nerve distal to ischial spine and obturator nerves and vessels.

The four compartments each have a central point and margins that overlap. The central axis of the anterior compartment is the urethra. For the central compartment, it is the tip of the coccyx and for the posterior compartment it is the third sacral vertebra. For the lateral compartment the central axis is the ischial spine. The extent of PE surgery is best defined by the compartments that are involved and resected to achieve an R0 margin.

Surgical Technique

As stated, the aim of surgery is to achieve an R0 resection margin as this offers the greatest survival benefit. The extent of resection performed depends upon the location of the tumour in the pelvis and whether the surrounding organs and structures are involved. If the primary or recurrence abuts another structure and there is doubt about obtaining a clear margin, then *en bloc* resection of the involved pelvic structure must be performed and this may include resection of part of the bony pelvis. In the setting of recurrent colorectal cancer, planes of dissection are ill-defined due to previous rectal dissection, resulting scar tissue and radiotherapy changes.

PE involves an abdominal approach that is combined with a perineal phase that can be conducted in either the lithotomy and/or prone position. Tumours in the anterior, central and lateral compartments are best resected through an abdominal combined with a perineal lithotomy approach. This position also works best for posterior tumours that involve resection of the sacrum at S3 or below where an abdominal approach gives better access and views than the prone position [43].

The level of sacral involvement dictates the surgical approach. Once there is tumour involvement of the S2 vertebra and above, a prone approach is required for a high sacrectomy due to the sacroiliac joint attachment. However, if only the anterior cortex of the midline bones of L5 and the upper sacrum need to be resected, this can be achieved abdominally.

Depending upon the number and type of pelvic organs involved, PE surgery requires a multidisciplinary team of highly skilled consultant surgeons from a number of surgical subspecialties including colorectal, vascular, urological, orthopaedic and plastic and reconstructive surgery. At our institution, colorectal surgeons predominantly perform the surgery, with other surgical disciplines being involved as necessary. Specialist anaesthetist and experienced theatre staff are also required and the procedure can take from 8 to 20 hours to complete (mean operating time of 9 hours at our institution).

Pelvic Exenteration: Abdominal Phase

Preoperative Preparation

Stoma sites are marked. If there is a plan for flap reconstruction of the perineum, the vertical rectus abdominis myocutaneous (VRAM) flap (which is the commonest type utilized) is marked with a surgical skin marker. If a colostomy is present, it is covered with a swab and an impervious plastic dressing for the duration of the PE or a clean stoma bag is applied and included in the preparation. Bowel preparation is recommended as long operating times and previous radiotherapy-damaged bowel may require repair. Bowel preparation can be omitted in patients with pre-existing stomas but the colon should be prepared if a colostomy is to be converted into a colonic conduit.

Patient Positioning

The patient is placed directly on a gel mattress so as to prevent slippage during steep Trendelenburg positioning. The abdominal phase of PE is performed in the modified Lloyd-Davies position with both arms secured by the patient's side. The perineal phase can be performed in modified Lloyd-Davies or in the prone position as dictated by the level of sacral involvement (*vide supra*). The anus, if present, should be sutured in order to prevent soiling and the vagina should be included in the skin preparation. Both the groin and thigh should be exposed and prepared if a vein graft harvest is anticipated for vascular reconstruction. If an abdominal sacrectomy is planned then the lumbosacral arch is elevated with a rolled towel to allow the whole sacrum to be free posteriorly [43].

Laparotomy

Laparotomy begins with a thorough evaluation to exclude metastatic peritoneal disease that may have been missed on preoperative CT, MRI and PET scans. Any nodules suspicious for peritoneal metastasis or other tissue suspicious for carcinoma should be sent for frozen section as confirmation of malignancy may change the course of the operation.

Meticulous adhesiolysis is performed and care is taken to prevent any enterotomies in irradiated small bowel. If there is no evidence of small-volume missed peritoneal disease, the planned exenteration can begin. Lateral pelvic side-wall involvement and bone fixity are no longer contraindications to resection where the extent of involvement is best assessed on preoperative MRI during the planning phase rather than by palpation during surgery.

Preparation of the Pelvis

The small bowel is mobilised out of the pelvis. Any small bowel loops adherent to tumour require *en bloc* resection with the exenteration specimen and are disconnected from the rest of the small bowel. The appendix, if still *in situ*, should be removed to prevent future difficulty with access after PE with a combination of stomas and abdominal wall mesh reconstruction.

The ureters are identified and ureterolysis is performed with adequate connective tissue to preserve the ureteric blood supply. Vessel loops are placed around them for identification. The ureters might be displaced from previous pelvis dissection and this is usually in a medial wards direction. The gonadal vessels are preserved if possible in male patients but they are ligated in female patients during radical hysterectomy. Preservation of the higher abdominal portion of the gonadal vessels is important for the ureteric blood supply to be maintained. Ligation of the gonadal vessels before the inguinal canal preserves the blood supply to the testes via collateral circulation. The pelvic portions of the ureters can be transected when an ileal conduit is planned.

Lateral pelvic side-wall lymph node dissection is routine with PE. This issue is discussed in greater detail in Chap. 17. The extent of lymphadenectomy generally includes nodes of the common iliac bifurcation, internal iliac chain and obturator nodes.

In PE with sacrectomy, a metal pin is inserted into the sacrum above the level of sacral involvement. This pin is then identified by image intensifier in the prone position, ensuring accuracy of the level of sacral transection (Fig. 16.2).

Pelvic Exenteration: Perineal Phase

The perineal phase can be performed via a wide lithotomy exposure or in the prone position or a combination of both.

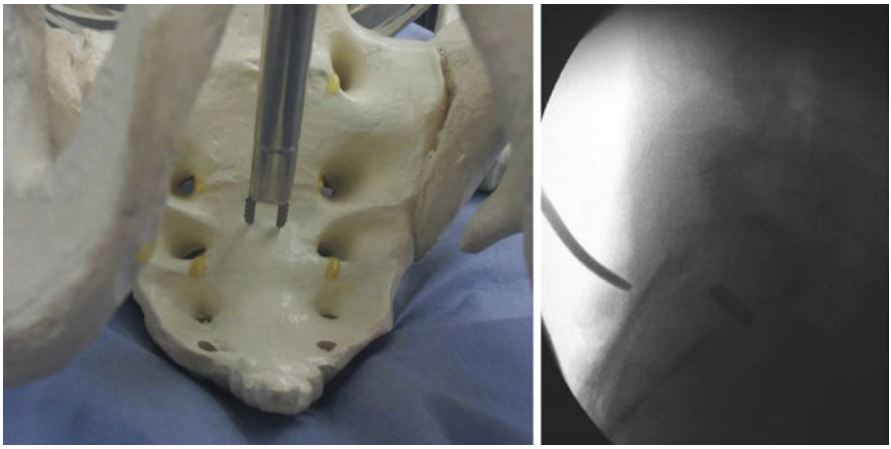

Fig. 16.2 Sacral pin insertion during the abdominal phase and assessment of the sacral pin position with an image intensifier. The patient lies in the prone position for sacrectomy in order to ensure accuracy of the level of the sacral transection

The prone position is used when an S2 or higher sacrectomy is required. The sacrectomy is the final step for the complete resection of the tumour. The *en bloc* specimen with transected sacrum is delivered and the perineal defect closed, commonly with a VRAM flap.

Surgical Approaches to Pelvic Exenteration

Anterior Pelvic Exenteration

Anterior compartment organs are involved, namely the bladder and adjacent reproductive organs. Mobilisation of the posterior (TME or presacral plane) and lateral planes (ischial spine to obturator internus muscles) should be performed prior to assessing the degree of anterior involvement and fixation to bony structures.

If the uterus and/or vagina is involved, a bilateral salpingo-oopherectomy, radical hysterectomy and either posterior or radical vaginectomy should be performed *en bloc* with both tumour and rectum. The level of tumour directs whether a restorative procedure is possible as opposed to a radical abdominoperineal resection. Depending upon the degree of vaginal/perineal resection, a myocutaneous flap reconstruction may be required rather than a primary vaginal closure with a flap favoured as these perineal wounds are typically large and have usually been previously irradiated [44].

Involvement of the bladder dome only can be treated with partial cystectomy *en bloc* with the tumour and rectum and primary closure of the bladder. If there is tumour involving the bladder trigone, prostate or membranous urethra, then a radical cystectomy or cystoprostatectomy with bowel conduit formation is necessary.

Radical Cystectomy (Male)

The bladder is mobilised. Anteriorly, the prevesical space of Retzius is opened and dissection is continued laterally to the endopelvic fascia and the levator muscles. The endopelvic fascia is opened so that the prostate can be elevated and in order to gain access to the dorsal venous complex. Once the dorsal venous complex is ligated, this permits mobilisation of the prostate inferiorly to the urethra. The urethra (as it exits the prostate and traverses the urogenital diaphragm) can be identified by palpating the urinary catheter. The membranous urethra is divided and the distal portion of the catheter removed. The distal cut portion of the urethra is then sutured closed.

For anterior tumours involving the urethra, urethrectomy may be performed in continuity from the perineum with transection of the urethra at the base of the penis. This allows *en bloc* resection of the membranous urethra and a more distal transection with a wider margin on the urethra and exposure down to the pubic symphysis (Fig. 16.3).

The vas deferens, superior vesical and inferior vesical vascular pedicles are ligated if they have not been already during the lateral pelvic wall dissection. Laterally, the obturator neurovascular bundle will be seen as it runs along the superior border of the obturator internus muscle. Bilateral obturator lymphadenectomy is performed with preservation of the neurovascular bundle. Anterior tumours require *en bloc* excision of the levators and the obturator internus muscles across to the ischial spine with or without preservation of the obturator neurovascular bundle and possible resection of the pubis.

If the rectum is *in situ* then dissection is continued along to Denonvillier's fascia. If bowel continuity is possible then an ultralow anterior resection is performed. If continuity is not feasible, then perineal dissection proceeds as per a wide abdominoperineal resection with the bone as the margins.

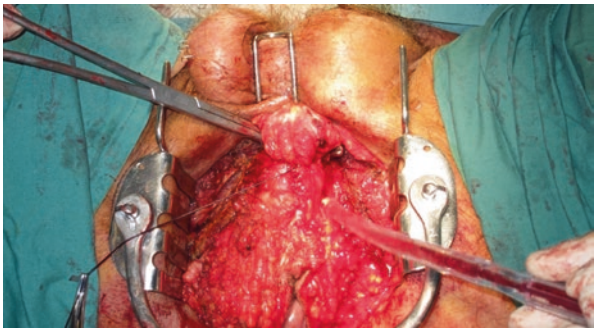

Fig. 16.3 Perineal urethrectomy with transection of the urethra at the base of the penis exposing the pubic symphysis

Radical Cystectomy (Female)

Mobilisation continues inferiorly after the ligation of the venous plexus. Palpating the urinary catheter identifies the urethra. The rest of the procedure is the same as in the male. The plane of resection for anteriorly-based tumours is adjacent to the inferior pubic rami and the symphysis with *en bloc* excision of the obturator internus, the levator muscle, bladder and vagina. This is performed in combination with a perineal lithotomy approach.

Anterior Tumours with Pubic Bone Involvement

For anterior compartment tumours abutting or infiltrating the pubic bone, a more radical margin is required. Lines of pubic bone transection are demonstrated in Fig. 16.1. The anterior levator muscles are exposed widely to the inferior ramus of the pubic bone and down to the ischial tuberosity from the perineum. The adductor and gracilis muscles are detached from their attachments to the lateral border of the inferior pubic rami.

It is possible to excise the pubic symphysis partially or completely *en bloc* with the tumour (Fig. 16.4). When the superior half of the pubic symphysis remains (transection along lines A and B), pelvic stability is maintained. If the entire pubic symphysis is excised (transection along lines B and C), pelvic stability is restored by a polypropylene mesh joining the cut ends of all four pubic rami. This is then covered with a myocutaneous or rotational flap.

Unpublished data from the Royal Prince Alfred Group in Sydney demonstrates an R0 resection rate of 63% in 54 cases of PE for locally recurrent rectal cancer requiring radical cystectomy. This improves to an R0 resection rate of 94% in a small group of patients (16) where *en bloc* excision of the pubic bone was performed.

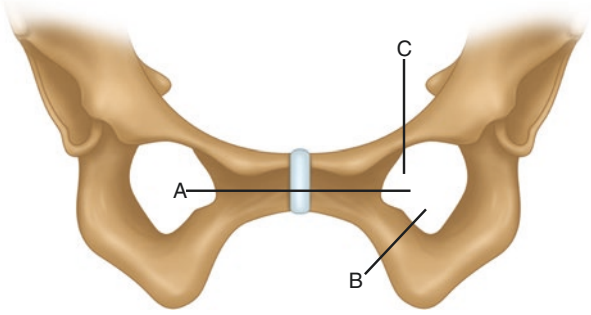

Fig. 16.4 Lines of pubic bone transection

Central Pelvic Exenteration

This is a group of tumours where a number of other structures may be involved. In female patients, central PE involves resection of the tumour with *en bloc* hysterectomy and posterior vaginectomy. The bladder and anterior wall of the vagina can usually be preserved. If these organs are involved then resection is extended into the anterior compartment as described above.

In patients where the dome of the bladder is involved, wedge resection with primary closure is performed. If a unilateral distal ureter is involved, then resection of the ureter and reimplantation with a Boari flap or a psoas hitch can be performed [45].

Posterior Pelvic Exenteration

In order to obtain clear margins, a sacrectomy may be necessary if the tumour invades the sacrum posteriorly. Sacrectomy does not have to be complete and in patients where the tumour only involves the sacral fascia, an anterior cortical or partial resection of the sacrum can be performed. This is best performed in the abdominal phase when only the anterior sacral body is excised and can be extended up to the level of L5. High complete sacrectomy (S2 and above) needs to be performed in the prone position. Sacrectomy from the S3 level and below can however, be performed via a combined abdominolithotomy approach. This approach has a number of advantages as it gives better access to the pelvic lateral compartments, allows better control of pelvic side-wall large vessels and offers better exposure to the ischium and the lumbosacral trunk as it exits the pelvis [43].

Sacrectomy can be performed at the S1/S2 junction without pelvic instability. After completion of the abdominal phase with reconstruction and abdominal wall closure, the patient is transferred to the prone jack-knife position for sacrectomy. During the abdominal part of the operation, a metallic pin is inserted into the sacrum at the level of the proposed sacrectomy (*vide supra*). Once prone, the pin can be confirmed by an image intensifier to ensure an accurate level of sacrectomy.

Sacrectomy from the S3/S4 junction and above usually requires proximal ligation of the internal iliac vessels. This devascularizes the pelvis and minimises haemorrhage. Arterial ligation distal to the first branch of the internal iliac artery is preferred so that skin and muscle flap (gluteus) healing is not significantly compromised. Bleeding from inadvertent injury to the internal iliac vessels, particularly venous bleeding can be significant at this stage. Low sacrectomy, requires distal ligation of the branches and tributaries of the internal iliac vessels at the level of transection.

During sacrectomy, especially proximal sacral transection, sacral nerves are sacrificed. Ligation of proximal sacral nerves (S1, S2) results in significant morbidity. Lower sacral nerves however, can be sacrificed with adequate limb function remain-

ing. The lumbosacral and S1 nerve root must be preserved to maintain good motor function to the ipsilateral lower limb. Gait without a foot-drop is secure if the majority of the sciatic nerve is preserved. A further advantage of a combined abdominolithotomy approach to sacrectomy is that it allows dissection of the sciatic nerve more laterally as it exits the greater sciatic foramen. Ligation of S2 and lower sacral nerves results in significant bladder dysfunction. Unilateral division usually results in only mild to moderate dysfunction, however, bilateral ligation results in an atonic bladder. Bladder dysfunction is further exacerbated by previous radiotherapy and surgery so that a sacrectomy above S3 may require a radical cystectomy with ileal conduit formation even in the absence of invasion into the bladder, prostate or seminal vesicles. Such a more extended procedure is performed as a quality of life decision in consultation with the patient.

Low posterior tumours require wide excision of the entire posterior pelvic floor from the level of the ischial spine laterally to the junction of the S3–4 vertebra medially (defined by the sacrospinous ligament at the deep margin). Excision of part of the piriformis muscle and sacral nerves laterally may also be required if there is tumour involvement. Once these structures have been disconnected laterally, the junction of S3 and S4 is exposed and the longitudinal ligaments and midline muscles are transected. The perineal surgeon then dissects posterior to the coccyx and sacrum up to the level of S3 prior to bone transection. Once, the sacral attachments are freed circumferentially, the sacrum is then transected trans-abdominally using a 20 mm extended length osteotome and hammer, from midline to lateral along the sacrospinous ligament to the ischial spine (Figs. 16.5 and 16.6). Prior to transection, the perineal surgeon dissects the gluteus attachments posteriorly free of the sacrum and places a second osteotome behind the sacrum to protect the skin from damage during the abdominal osteotome transection [43] (Fig. 16.7).

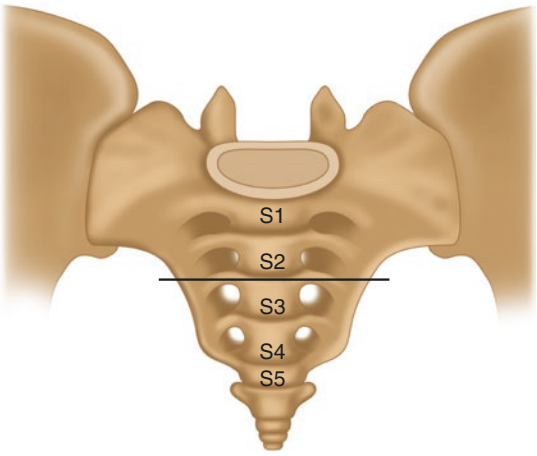

Fig. 16.5 Line of sacral transection from S3 down performed in combined abdominolithotomy approach

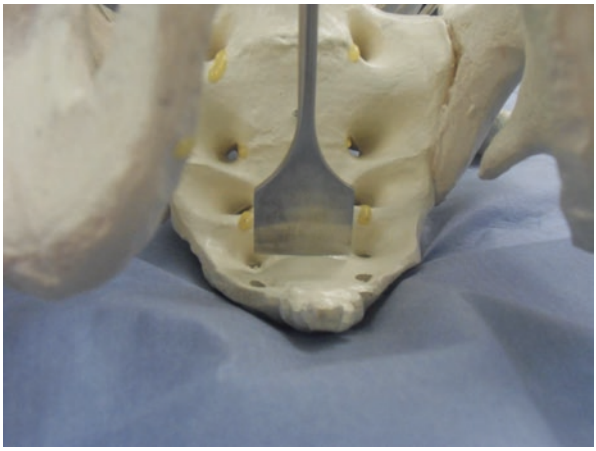

Fig. 16.6 Abdominal osteotome position for S3/S4 level sacrectomy in abdominolithotomy position

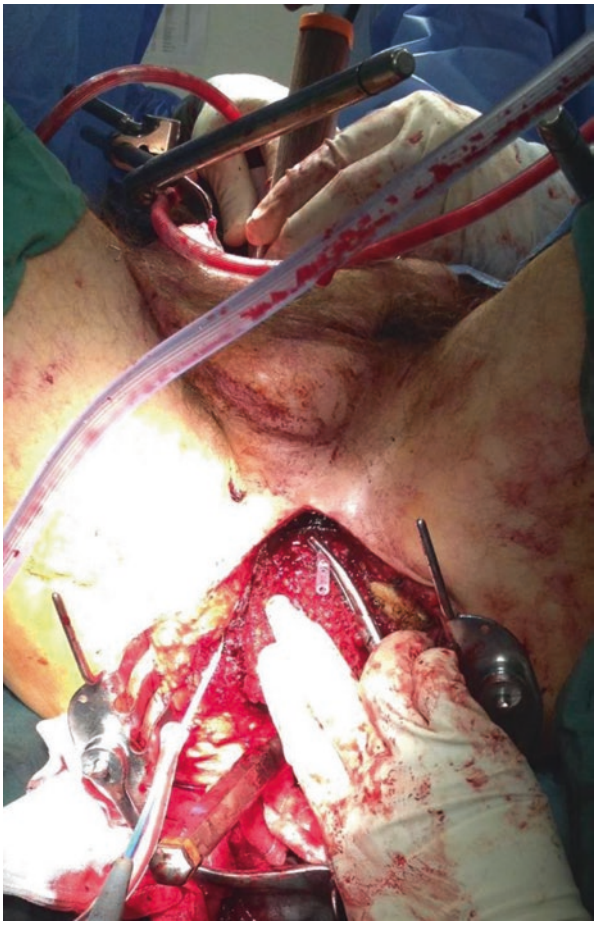

Fig. 16.7 Abdominal and perineal osteotomes prior to sacral transection in abdominolithotomy position

Lateral Pelvic Exenteration

Tumours with pelvic side-wall invasion are considered the most challenging and until recently, PE surgery was contraindicated in these cases [39]. This is no longer the case with encouraging results from the Royal Prince Alfred Group in Sydney that demonstrate achievable R0 resection rates of 53% in lateral compartment malignancies [31]. The anatomical approach to lateral tumours is in the plane lateral to the internal iliac vessels. This plane allows access for dissection and excision *en bloc* of the lateral pelvic structures: obturator internus and piriformis muscles, sacrotuberous and sacrospinous ligaments and sacral nerve roots.

Lateral dissection begins by mobilising the pelvic ureters medially. If one or both ureters are involved, a decision is made whether re-implantation into the bladder or, ileal or colonic conduit with radical cystectomy is most appropriate. If there is no evidence of involvement, ureterolysis is performed from the pelvic brim to the bladder and a vessel loop is placed around the ureter for identification.

Ureterolysis is followed by vascular isolation and ligation of the internal iliac artery. After dissection of the common iliac artery and vein, the course of the external iliac artery and vein is dissected to the inguinal ligament and the relationship of these vessels to the tumour is assessed. If there is involvement, a decision is made whether partial or complete resection of the vessels and patch or interposition grafting is necessary usually with the assistance of a vascular surgeon. Arterial reconstruction is best performed immediately, to avoid compartment syndrome of the limb.

Next, the origin of the internal iliac artery is identified and proximally controlled with a vessel loop. It is preferable, if possible, to ligate distal to the first branch of the internal iliac artery so as to maximise healing of the skin and gluteal muscles in the buttock region. In order to get safe access to both the internal iliac vein and the common iliac vein and prior to freeing of the external iliac vessels, the internal iliac artery must be divided first. This is then followed with division of the internal iliac vein allowing access to the other vessels covered by it. The distal lateral branches of the internal iliac vessels are ligated individually and resected *en bloc* with the tumour mass.

Division of the internal iliac vessels exposes the lumbosacral trunk and the sacral nerve roots (S1, S2, S3) as they converge to form the sciatic nerve at the ischial spine (Fig. 16.8). These structures lie behind the fascia overlying the piriformis muscle. Lateral pelvic side-wall tumours may involve the sacral nerve roots and the sciatic nerve. The sciatic nerve can be sacrificed if necessary for an R0 resection margin but this results in an altered gait and requires an orthotic aid for the ankle joint. Sciatic nerve trunks are dissected out and retracted laterally allowing resection of muscle and pelvic bone if and as necessary. The ischial spine can be resected in order to gain maximal lateral exposure and to reveal the sciatic nerve as it exits the pelvis via the greater sciatic foramen. This also helps free the lateral aspect of the sacrum by releasing the coccygeus muscle with the sacrospinous ligament, a step that aids with sacrectomy if required. If there is bony or ligament involvement anterolaterally along the greater sciatic notch, the ischial spine or the lesser sciatic

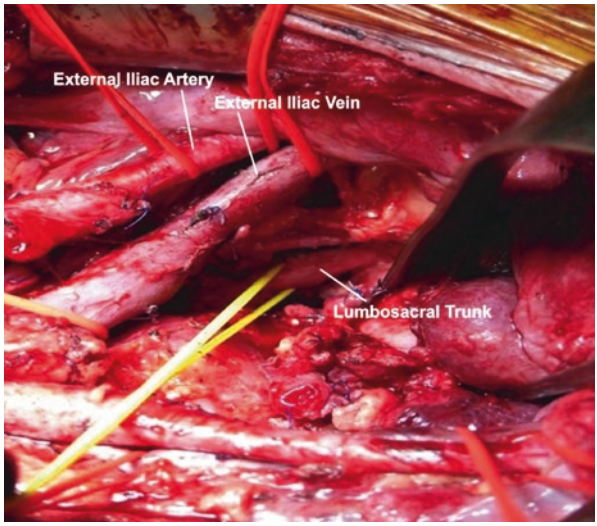

Fig. 16.8 Division of the internal iliac artery and vein to expose the lumbosacral trunk

notch, the involved section of bone and sacrospinous and sacrotuberous ligaments are removed *en bloc* using an osteotome and diathermy. The remainder of the dissection continues anteriorly or posteriorly depending upon the extent of the tumour.

Perineal Reconstruction

The perineal defect can be closed primarily or with a pedicle flap. The advantages of myocutaneous flaps are that they provide protection to the small bowel and prevent perineal herniation with a generally improved primary wound healing and less perineal morbidity [44]. Prolonged hospital stay in such cases is associated with patient condition (e.g. an underweight status preoperatively) but is also dependent upon the presence of postoperative infection and anastomotic leak/fistulas, particularly where patients experience more than one type of postoperative infection [46] or where they require multiple out-of-discipline consultations.

The most common types of flap used include a VRAM flap, gracilis myocutaneous flap and gluteal myocutaneous rotational flap. The VRAM flap provides good tissue bulk for perineal and sacral defects and is easier to swing into the perineal or sacral space when compared with other flaps. An additional advantage is that they provide non-irradiated, well vascularised tissue to a region prone to healing problems. Difficulties may be encountered where there is a current or a previous stoma and where prior abdominal incisions especially transverse incisions such as open appendicectomy or open inguinal hernia repairs have been previously performed. Morbidly obese patients and those patients with vascular disease can have non-patent or diseased epigastric vessels and this matter should specifically be checked with a CT angiogram prior to surgery. Furthermore, rotation and transfer of a VRAM flap in an obese patient may be technically demanding due to the subcutaneous fatty

bulk of the flap as it is transferred through a small pelvic bony diameter, resulting in greater tension on the entire flap. A gluteus maximus V-Y flap is a better option in the morbidly obese case providing that the gluteal vessels have not been ligated off the internal iliacs.

Gracilis myocutaneous flaps are generally less robust and are usually too small to fill exenteration wounds. Gluteus maximus myocutaneous flaps can be utilised for prone defects but should be avoided if lateral internal iliac artery division has been performed as they are then devascularised and rely on collaterals.

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Chapter 17
The Role of Lateral Pelvic Node Dissection in Rectal Cancer Surgery

A Review of the Experience in Japan-

Fumio Konishi and Tsuyoshi Konishi

Introduction

Over time there have been significant differences in the surgical management of rectal cancers between Japan and Western countries. In the Western world, preoperative chemoradiation and total mesorectal excision (TME) have become the standards in an attempt to reduce the locoregional recurrence rate and to improve long-term cancer-specific outcomes. A similar view concerning cancer aims has occurred in Japan where mesorectal excision is often routinely performed in concert with lateral pelvic lymph node dissection (LPND) for low rectal cancers. In 1993 Heald et al. [1] described the technique of TME and highlighted the importance of complete excision of the mesorectum for tumours of the mid- and lower rectum. A similar approach had been adopted by Japanese colorectal surgeons even before TME was introduced by Heald. A difference in mesorectal dissection between the two environments, however, is the "Tumor Specific Mesorectal Excision (TSME)" which is commonly performed in Japan [2] where the mesorectum is not completely excised down to the pelvic floor in selected cases [3]. The decision whether to perform a TME or a TSME is dependent upon the level of the tumour although the fundamental concept of appropriate mesorectal dissection (in the mesorectal plane) is similar between Japan and other Western countries. This view is allied to the known benefits of selective preoperative chemo-radiation prior to TME where

F. Konishi (✉)
Department of Surgery, Nerima Hikarigaoka Hospital, Tokyo, Japan
e-mail: DZD00740@nifty.ne.jp

T. Konishi
Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

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literature consistently shows lower locoregional recurrence rates when preoperative chemo-radiation was added to TME. Despite this, however, the long-term benefits of preoperative chemo-radiation remain to be fully established [4].

Lateral pelvic lymph node dissection was first described and attempted in the Western world in 1950s, however, it was abandoned early on because of significant postoperative functional disabilities and an unproven survival benefit [5–7]. Enker et al. [8] reported the survival benefit for carrying out selective LPND in 1986 showing, in an era that preceded TME, that there was survival benefit by *en bloc* pelvic lymphadenectomy over conventional resection particularly for Dukes' C cases. The National Cancer Institute sponsored a panel of experts (in line with the methodology used by the American Society of Clinical Oncology) to systematically review the current literature and to draft guidelines for rectal cancer management in 2001 [9]. In their recommendations, they stated that "in the context of clinically suspected lateral lymph node disease, the dissection should attempt to remove these nodes, as is technically feasible." The level of evidence was, however, inconsistent (Grade C) where LPND has not been widely accepted in Western countries. By contrast, Japanese experience has consistently shown a survival benefit for the performance of LPND since the late 1970s where the technique has become part of main stream surgical management for cancers of the lower rectum [10]. This comparative approach has shown similar rates of local recurrence when assessed against neoadjuvant chemoradiation and TME [11]. In this regard, the Japan Clinical Oncology Group (JCOG) has conducted a randomized controlled clinical trial (JCOG 0212) which has confirmed the non-inferiority of the TME + PLND approach over TME for Stage II/III rectal cancer cases where there was suspected lateral pelvic node metastasis [12].

Anatomy of the Regional Lymph Nodes in Rectal Cancer Surgery

In general, the main route of lymphatic flow of the rectum is considered to be along the superior rectal artery up to the origin of the inferior mesenteric artery (IMA) resulting in an upward lymphatic drainage. The upper limit of lymph node dissection for this flow route is the lymph nodes around the origin of the IMA. The other important point of lymphatic flow is along the internal iliac artery. According to the Japanese classification of colorectal cancer, in D3 lymph node dissection for low cases, the regional lymph nodes should be dissected and include the nodes along the IMA as well as the lateral pelvic nodes along the internal iliac artery and the obturator area/neurovascular bundle [13]. The lateral pelvic nodes include those nodes lying along the internal iliac artery (#263), as well as the obturator artery and nerve (#283), the common iliac artery (#273) and the external iliac artery (#293). Nodes along the internal iliac artery are further subdivided into two discrete regions; namely, those proximal to the division/take-off of the superior vesical artery (#263p)

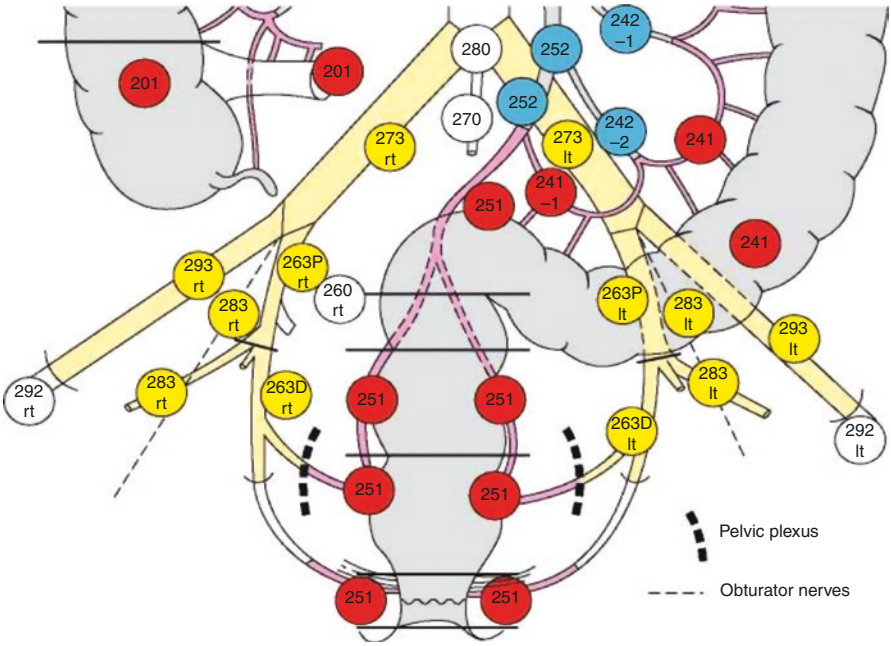

Fig. 17.1 The yellow circles represent the lateral lymph nodes as defined by the Japanese Classification of Colorectal Carcinoma [13]. These are constituted by the internal iliac, common iliac, obturator and external iliac nodal groups. The red circle categories are the pericolic and perirectal nodes and the blue circles represent intermediate lymph nodes along the major vessels

and those distal to that point (#263d). The numbers in parentheses are the station numbers which have been allocated in accordance with the Japanese classification system [13]. These stations are graphically represented in Fig. 17.1.

Initial Experience of Lateral Pelvic Lymph Node Dissection (LPND) in Japan

The initial results of LPND for low rectal cancer were reported by Hojo et al. [14], Koyama et al. [15] and Moriya and colleagues [16] in early 1980s, all authors being surgeons working at the National Cancer Center in Tokyo. The procedures in these earlier reports included extended dissections of the lateral pelvic side-wall lymph nodes with selected resection of part of the internal iliac artery. This type of dissection necessitated an extensive exposure of the aorta along with the external and internal iliac vessels and often included a resection of the autonomic nerves *en bloc* including the superior hypogastric plexus, the hypogastric nerves and the pelvic plexi. Consequently, the initial trials for dissection included para-aortic nodes (station number 216), nodes of the aortic bifurcation (#280), common iliac nodes

(#273), the external iliac chain (#293), internal iliac nodes (#263) and the obturator group (#283). In these cases, not unexpectedly, the operative times were longer (mean: 390 min) with a higher (and substantial) comparative peri-operative blood loss (mean: 2100 mL).

In the study reported by Koyama et al. [15] of patients with rectal cancer, extended lymph node dissection for curative intent (which included the lateral pelvic lymph nodes), was performed in 163 patients and compared with historical controls not undergoing an extended systematic lymphadenectomy (high ligation of the IMA and meticulous dissection of the abdominopelvic lymphatic system). The 5-year survival rates for those with or without extended lymph node dissection were 83.2% *vs*. 63.7% in Dukes B cases and 52.5% *vs*. 30.8% in Dukes C cases. The cumulative local failure rate was decreased from 26.1% down to 8.4% in the Dukes' B patients and from 44.3% down to 24.5% in the Dukes C cases. As a result of extensive lymph node dissection, however, there was significant disturbance of urinary and sexual functions which occurred in nearly all the patients with frequently a reversible urinary dysfunction but irreversible impotence in the male patients [17].

LPND with Autonomic Nerve Preservation

In the second phase of lateral pelvic lymph node dissection in Japan, the preservation of urinary and sexual function became paramount, where the autonomic nerves including the superior hypogastric plexus, hypogastric nerves, pelvic splanchnic nerves and the pelvic plexi were totally or partially preserved. In this regard, Sugihara and Moriya first reported the results of 214 patients who underwent pelvic node dissection with complete and partial autonomic nerve preservation (depending upon the extent of tumour invasion) [18]. Over a median follow-up period of 53 months, the local recurrence rate was 5.6% overall. The 5-year survival rates for Dukes Stage A (n = 551), Dukes Stage B (n = 72), and Dukes Stage C (n = 87) patients were 96.4%, 84.0%, and 67.3% respectively. Among patients undergoing preservation of the unilateral pelvic plexus alone, 93.5% maintained the ability to void spontaneously. Amongst those patients who had complete preservation of the autonomic nerve system, 70.4% of male patients maintained male sexual function and among those patients who had the hypogastric nerves removed with preservation of the pelvic nerve plexi, 66.7% were capable of erection and intercourse, although without normal ejaculation. Briefly, autonomic preserving surgery results in an extent of LPND which includes station numbers 273, 263 and 283 where the extent of the LPND is more limited than that of the initial reports by Hojo et al. [14] and Koyama et al. [15].

Autonomic nerve preserving surgery and LPND for low rectal cancer was also reported by Mori et al. [19] and Shirouzu and colleagues [20] with similar results,

where the latter study showed a reduction in local recurrence rate and an improvement in 5-year cancer-specific survival particularly in Dukes' C cases subjected to TME combined with autonomic nerve preservation and lateral lymphadenectomy. Due to the favorable long-term outcome and acceptable functional results, autonomic nerve sparing surgery and LPND has become a standard procedure for low rectal cancer in Japan.

The Current Technique of LPND

Sugihara and colleagues [21] reported a multi-institutional retrospective study involving 117 patients with lateral pelvic nodal metastases. The distribution of lateral pelvic node metastasis was mostly confined to the internal iliac area and the obturator region (#263p; 26%, #263d; 47%, #283; 38%) where only 7.7% of the metastases were detected in other areas. As a result of their experience, lymph nodes around the internal iliac artery (#263p and #263d) and the obturator artery and nerve (#283) are always dissected as part of a standard LPND. The LPND procedure (as described) is typically performed following rectal resection (either as a TME of a TSME). Initially, both ureters are freed, encircled with tape and then retracted medially and both hypogastric nerves are also exposed and retracted medially. All fatty tissue surrounding the internal iliac artery and in between the internal (#263p) and external iliac arteries (#293) is dissected distally from the point of bifurcation of both arteries. The fatty tissue along the external iliac artery is dissected medially and that along the external iliac vein is dissected to expose and clear the iliopsoas muscle. In this part of the procedure, the obturator region is exposed and the fatty tissue with the lymph nodes surrounding the neurovascular bundle as it goes through the obturator canal is meticulously dissected (#283).

Following the obturator dissection skeletonizing the obturator nerve and artery, the piriformis muscle and part of the sacral plexus (the lumbosacral trunk; L4, 5) on the pelvic side-wall, the caudal end of the obturator dissection reaches the space lateral to the urinary bladder. Internal iliac lymph node dissection is performed distally to the level of the superior vesical artery take-off (#263p) continuing the dissection of the tissue along the internal iliac artery continues further on down exposing the branches of the anterior and initial posterior divisions of the internal iliac artery. The pelvic plexus is located medial to the internal iliac artery and the fatty tissue between these two main structures should be completely dissected (#263D) (Fig. 17.2; Video Link: https://doi.org/10.1007/s00464-010-1531-y).

During the process the branches of the internal iliac artery such as inferior vesical artery and internal pudendal artery are exposed with preservation of the pelvic plexus and the pelvic splanchnic nerves (S3, 4). This completes the lateral pelvic node dissection. As an optional procedure, when there are swollen nodes around the

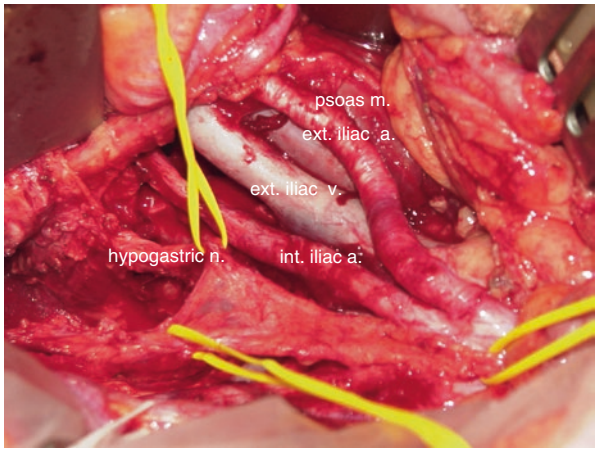

Fig. 17.2 Lateral pelvic node dissection in open surgery

internal iliac artery, the artery is ligated and resected in order to complete the lymph node dissection. These dissections may be performed laparoscopically [22] or robotically [23] with an equivalent number of lymph nodes retrieved and a similar operating time but with a lower estimated blood loss using the robot.

The Long-Term Outcome of Low Rectal Cancer Patients Who Underwent LPND: Single Institutional and Multi-Institutional Cohort Studies

Table 17.1 shows nine previous reports outlining the long-term outcome of rectal cancer patients who underwent lateral pelvic lymph node dissection. These reports include both initial extended lymph node dissections as well as autonomic nerve preserving surgery. All the reports except for one by Sugihara et al. in 2006 [21] were single institutional studies [14, 16, 18, 19, 24–27]. The locations of the tumours in the reports were either low rectum or low and mid-rectum. The percentage of lateral pelvic node metastasis ranged from 9% to 27%, and the 5-year survival rate of those with lateral pelvic node metastasis following curative surgery ranged from 25% to 49% overall. The data were analyzed, under the assumption that if LPND is not performed then all the cases with positive lateral pelvic nodes cannot survive for 5 years resulting in a survival benefit for the performance of LPND ranging from 2.8% to 8.8%.

The only multicenter study amongst this group collected the data of rectal cancer patients who underwent surgery from 12 institutions over the period between 1991 and 1998 [21]. In this analysis, of 1977 patients with rectal tumors in the upper and lower rectum (with exclusion of recto-sigmoid cancers), 930 underwent LPND without adjuvant chemo-radiotherapy. Lateral pelvic node metastases were found in

Table 17.1 Long term outcome of rectal cancer surgery with lateral pelvic node dissection: survival benefit *2.8–8.8%*

Author (Ref)	Year	Site of tumor	LPN met (%)	5 year survival rate (%) of LPN met. cases	Survival benefit of LPND (%)
Hojo [14]	1982	Lower rectum	23	25	5.7
Moriya [16]	1989	Lower rectum	18	49	8.8
Sugihara [18]	1996	Mid-lower rectum	14	49	6.9
Moriya [24]	1997	Lower rectum	14	43	6.0
Hida [25]	1997	Mid-lower rectum	11	25	2.8
Mori [19]	1998	Lower rectum	13	37	4.8
Takahashi [26]	2000	Mid-lower rectum	9	42	3.8
Fujita [27]	2003	Lower rectum	27	28	7.6
Sugihara [21]	2006	Mid-lower rectum	14	46	8.3

129 cases (13.8%) of the total cohort. Regarding lower rectal cancer, lateral pelvic node metastases were found in 117 of 1272 patients (14.9%). The disease-free survival (DFS) of low rectal cancer cases with or without LPND was 87.0% and 67.6%, respectively (P = 0.0026) for stage II cases. By contrast, the DFS of those with or without LPND in stage III low rectal cancers did not show any statistically significant differences (61.2% *vs.* 65.6%, respectively). The authors analyzed the effect of pelvic lymph node dissection by multiplying the rate of positive lateral pelvic nodes by the 5-year survival rate of patients with positive lateral pelvic lymphadenopathy, concluding that LPND would improve the 5-year survival rate of T3–4 low rectal tumors by about 8% overall. This would suggest that LPND may be indicated for these T3–4 tumours with a higher-risk patients of positive lateral lymph nodes.

Factors Predictive of Lateral Pelvic Lymph Node Metastasis: Indications for Lateral Pelvic Lymph Node Dissection

According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) 2010 "Guidelines for the treatment of colorectal cancer" [28], LPND is indicated when the lower border of the tumor is located distal to the peritoneal reflection and when the tumor invades beyond the muscularis propria (Fig. 17.3). A multivariate analysis of the cohort study by Sugihara et al. [21] showed that female gender, moderately or poorly differentiated adenocarcinoma, a low rectal tumour, tumour size ≧4 cm and T3–4 stage tumors were each significantly associated with an increased incidence of positive lateral pelvic node metastasis. Among these significant factors "a low rectal tumour" and "T3–4 Stage" demonstrated the higher hazard ratios.

These data are consistent with the indication for lateral pelvic lymph node dissection in the Japanese guidelines. Another important factor for the prediction of lateral pelvic node metastasis is the CT/MRI diagnosis of lymph node metastasis. In

Fig. 17.3 Indication for LPND. JSCCR 2010 "Guidelines for the treatment of colorectal cancer" [28, 47]

this respect, Brown et al. [29] reported the diagnosis of lymph node metastasis using MRI and stated that although the size of the node on MRI is not important, the morphological findings are; most notably, a mixed signal intensity with border irregularity. However, other groups have reported that the size of the depicted lymph nodes is actually the most important predictor for metastasis. The cut-off point regarding the size of the lymph node for the prediction of metastasis has ranged from 5 to 10 mms without a widely accepted consensus [30–33].

In Japan, there are two main opinions regarding the indications for performance of a LPND. One (as stated above) is to perform the LPND when the lower margin of the tumor is located below the peritoneal reflection (low rectal tumor) and when the cT staging is either cT3 or cT4 regardless of the size of the nodes detected on CT or MRI. The other indication is to perform the procedure when the above two criteria are fulfilled and enlarged lateral pelvic lymph nodes are present on CT/MRI. There is in this regard, currently no consensus regarding which of these two criteria is most appropriate with one recent trial addressing the survival benefit for LPND when there are preoperatively detected nodes [34].

A Randomized Controlled Trial Comparing Mesorectal Excision with and Without LPND (JCOG-0212)

As mentioned in the previous sections, after performing LPND for the abovementioned indication the 5-year survival rate may improve by 8–9%. Although the survival benefit for the performance of LPND has been shown in a number of reports by Japanese surgeons, none of these studies were randomized controlled clinical trials and thus at present the benefits of performing LPND are still inconclusive. In 2003, the Japanese Clinical Oncology Group (JCOG) commenced a randomized controlled trial [12] comparing mesorectal excision (ME) with and without LPND. In this trial, neither group of patients received preoperative chemo-radiation and as a result, the trial did not compare the Western management standard of TME plus preoperative chemo-radiation with the Japanese standard (ME plus LPND without preoperative chemo-radiation). In the Japanese trial, the inclusion criteria were based upon Sugihara et al. [21] incorporating those cases deemed high risk for lateral pelvic lymph nodes; namely, (1) rectal cancers of clinical stage II or III, (2) tumours with a distal margin below the peritoneal reflection and (3) cases without

preoperative lateral pelvic lymph node enlargement on CT/MRI (nodes ≥10 mm, strongly suspicious).

After the operating surgeons had confirmed the potential of an R0 resection during surgery, the patients were intra-operatively randomized either to an ME alone or an ME with LPND. The mesorectum with at least a 4 cm clearance margin was resected, so that a TME was performed when the length of the mesorectum distal to the tumor was <4 cm. In this trial, ME plus LPND was considered to be the standard treatment and ME alone was tested in order to determine whether this approach was non-inferior concerning long-term outcome compared with combined ME plus LPND. There were 33 major hospital participants in the trial throughout Japan with a total of 701 patients accrued between June 2003 and August 2010. The patients were assigned to ME alone (n = 350) or ME plus LPND (n = 351). The primary endpoint was the relapse-free survival rate.

The short-term outcome was reported in 2012. The operation time was significantly longer in the ME with LPND group when compared with the ME alone group (360 min *vs.* 254 min, respectively; $P < 0.001$). The mean amount of blood loss was also significantly higher in the ME plus LPND group when compared with the ME alone group (576 mL *vs.* 337 mL, respectively; $P < 0.001$). Grade 3–4 postoperative complications tended to occur more frequently in the ME plus LPND group than in the ME alone group (22% *vs.* 16% respectively) with a higher surgical reintervention rate in the ME + LPND combined group. Regarding the lymph node metastasis rate, 26 (7%) patients had lateral pelvic lymph node metastases amongst the cohort of 351 patients who underwent ME plus LPND. This percentage is considered to be somewhat lower than that expected and it is uncertain whether this may be a confounding factor affecting any survival benefit attributable to lateral pelvic node dissection in any long-term follow-up analysis. Interim analysis of male sexual function, in 2016 showed that LPND did not increase the risk of dysfunction reported by the patients (ME alone 68%, 17/25 [95% CI: 47–85%] *vs.* 79%, 23/29 [95% CI: 60–92%]; $p = 0.37$). In this study, age was the only factor predictive of sexual dysfunction after surgery where the incidence of preoperative erectile problems was similar between the two groups [35].

Can Preoperative Chemo-radiation Be an Alternative Treatment for LPND?

In Japan, LPND has been widely accepted as a surgical method for managing low rectal cancer and preoperative chemo-radiation has not been part of standard therapy. In this sense, there are only a limited number of reports comparing LPND with preoperative chemo-radiation. Watanabe et al. [36] retrospectively analyzed 150 rectal cancer patients who underwent rectal resection with or without preoperative radiotherapy in combination with LPND. They reported that there were no significant differences in the long-term outcome between preoperative radiation without

LPND and LPND without preoperative-radiation and the authors suggested that for Japanese practice, preoperative radiotherapy can be an alternative therapy in place of LPND for patients with lower rectal cancer. Similarly, Nagawa et al. [37] reported a small scale randomized controlled trial comparing preoperative radiation with and without LPND. In this study, there was no difference in the overall survival and disease-free survival between the two groups and the authors concluded that LPND is not necessary as a curability option for patients with advanced carcinoma of the lower rectum who undergo preoperative radiotherapy. Both of these reports have suggested that preoperative radiation can be substituted as an alternative to LPND potentially reducing the risk of functional postoperative disability (urinary disturbance and erectile dysfunction/impotence) although larger patient numbers are required to make such a definitive judgment.

In 2008, Kim et al. [31] analyzed the long-term outcome of 366 patients who underwent preoperative chemo-radiation without LPND and determined that lateral pelvic recurrence was a major type of loco-regionally recurrent disease. The authors concluded that preoperative chemo-radiation may not be sufficient to sterilize the metastatic lateral pelvic nodes. In this respect, Akiyoshi et al. [33] analyzed 127 patients who underwent preoperative chemo-radiation. In their study, LPND was performed only in the ypN positive cases. As a consequence, there were no local recurrences in the LPND group, however there were 3 cases with local recurrence among those not undergoing LPND. Despite the small numbers, the authors concluded that in selected cases LPND may be necessary even in those patients who received preoperative chemo-radiation. At present, because of these contradictory results, the necessity of LPND in patients who have received preoperative chemo-radiation is still unclear.

LPND in Laparoscopic Surgery

Laparoscopic colorectal surgery was first performed in early 1990s in both Japan and the Western world and has become one of the standard procedures for the surgical treatment of colorectal cancer. As Fig. 17.4 shows there has been a steep rise in the number of laparoscopic colorectal surgeries performed for cancer in Japan. Although the number of laparoscopic rectal cancer surgeries has not risen as fast as laparoscopic colon cancer surgery, there has nevertheless been a recent rise in laparoscopic rectal cancer cases in Japan. According to a nationwide survey conducted by the Japan Society of Endoscopic Surgery, the take- up rate of laparoscopic rectal cancer surgery rose up to 50% in 2013. As with open surgery for tumours in the lower rectum with T stage II or III, laparoscopic LPND may be indicated.

The use of laparoscopic LPND was first reported in 2011 by Konishi T, et al. [22, 38].

The authors reported their initial experience of 14 cases [22]. All the cases in the report were those with enlarged lateral pelvic lymph nodes on CT/MRI. The mean

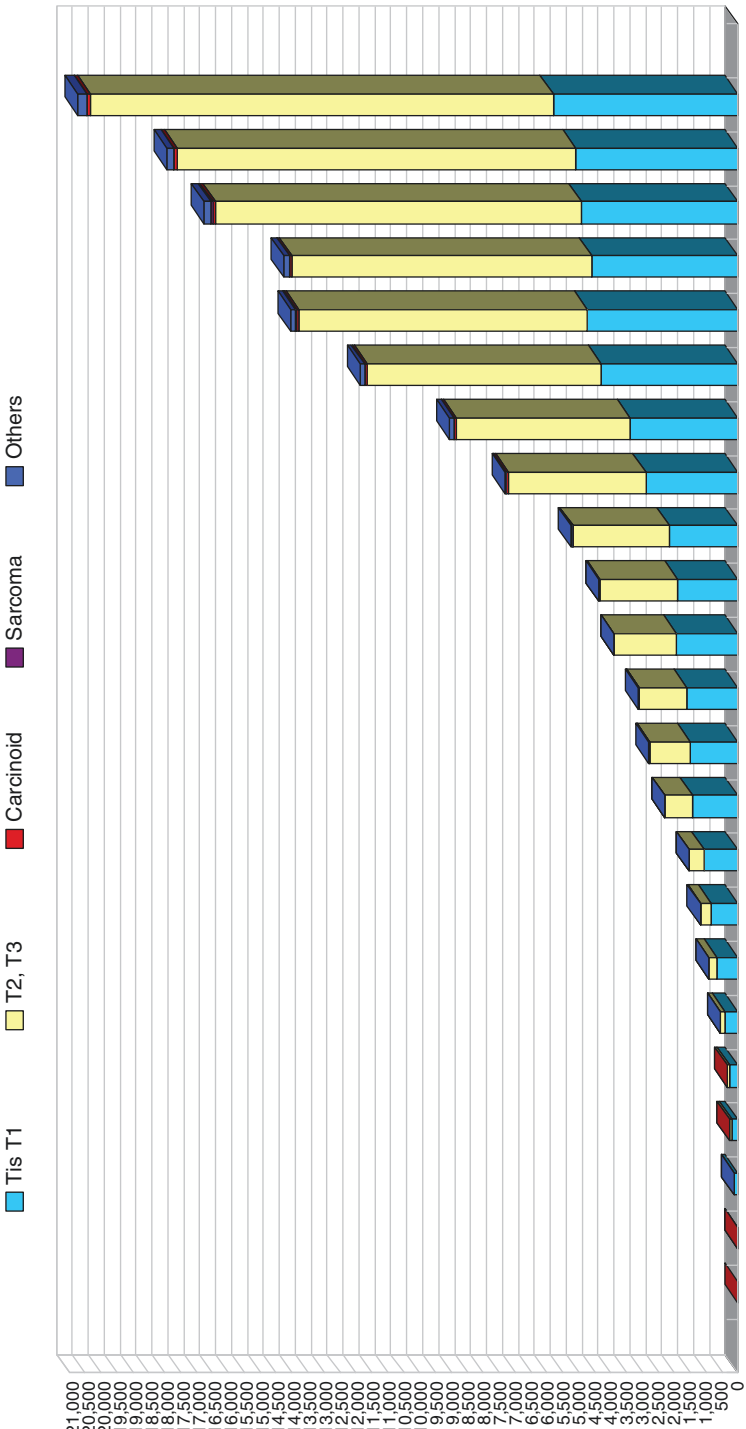

Fig. 17.4 Number of laparoscopic colorectal cancer surgeries in Japan. 1990–2013 Nationwide survey performed by Japan Society of Endoscopic Surgery (2014)

operative time was 413 min and there were no cases of conversion to open surgery. Thereafter several Japanese, Korean and Chinese surgeons have reported their initial experience with laparoscopic LPND as shown in Table 17.2 [38–45]. The largest series was that reported by Liu et al. [41] where the mean operating time of the entire procedures was 271 min. Kagawa et al. [44] reported the initial Japanese experience with 50 cases of LPND using the robot with a similar study by Yamaguchi et al. [46] showing advantage of the robot-assisted laparoscopic hybrid technique over open surgery with a higher rate of sphincter preservation using the robot and a lower mean operative blood loss. In this study, the rates of wound infection, small bowel obstruction, anastomotic leakage and urinary retention were also significantly less when the robot was used but the numbers of harvested lymph nodes and positive resection margins were equivalent between the two groups. In general, laparoscopic (or minimally invasive) LPND (as shown in Fig. 17.5) provides a better exposure and surgical view of the anatomy than open surgery (on the proviso that the principal operator and the assistants are well trained). Minimally invasive approaches for LPND require further work so as to assess the functional outcomes of nerve-sparing techniques. The disadvantage of this approach is that it is technically far more demanding and training in the techniques are not particularly easy because of the relatively low number of cases where laparoscopic or robotic LPND is indicated. Although the availability of the technique remains limited, laparoscopic LPND will likely become the accepted practice.

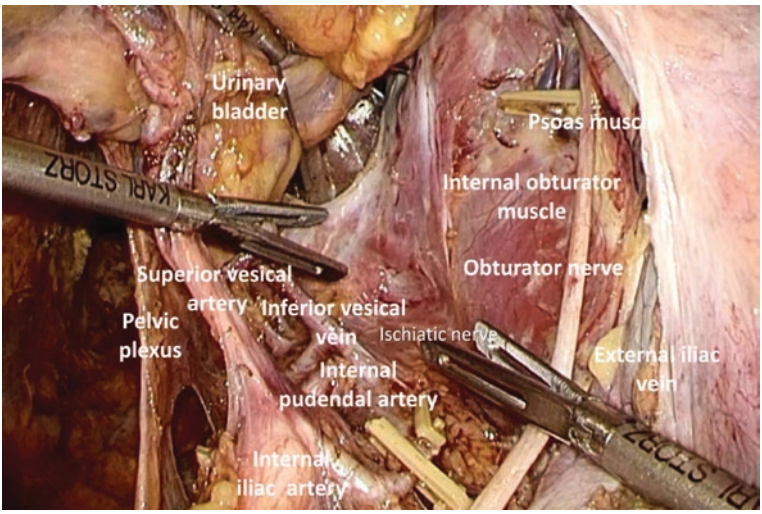

Fig. 17.5 Lateral pelvic node dissection with autonomic nerve preservation in laparoscopic surgery (right side)

Table 17.2 Reports on laparoscopic/robotic lateral pelvic node dissection

	Year of report	Lap/robotic	Number of cases	Op. time (min)	Blood loss (mL)	Post-op stay (days)	Conversion to open
Konishi T [38]	2009	Lap	14	413	25	–	0
Liang T [39]	2011	Lap	34	–	–	9	–
Park J [40]	2011	Lap (14)/ Robotic (2)	16	322	188	9.9	0
Liu T [41]	2011	Lap	68	271	150	11.5	–
Obara S [42]	2012	Lap	12	678	155/1217	–	–
Kagawa H [44]	2014	Robotics	50	476	27	8	0
Furuhata T [45]	2014	Lap	18	604	379	25.5	0
Bae S [43]	2014	Lap (10)/ Robotic (11)	21	396	200	10	0

Future Prospects

The controversy whether the preoperative chemo radiation plus TME is superior or equivalent to ME plus lateral pelvic node dissection will not likely be solved in the near future. However, the long-term results of the randomized controlled trial (JCOG0212) comparing ME with ME plus lateral pelvic node dissection is expected to soon provide vital information concerning the preferred approach in low advanced rectal cancer. If the superiority of the latter technique is proven or non-inferiority of the ME alone approach is not proven, then lateral pelvic lymph node dissection will likely be chosen as a standard treatment in Japan for Stage II and III low rectal cancer. Future extended multi-institutional studies may permit such an approach to be translated to other countries in the Western world.

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Part V
Radiation Therapy

Chapter 18
The Surgeon's Perspective on Radiation Therapy

Joakim Folkesson, Åsa Collin, and Lars Påhlman†

Introduction

Modern treatment of rectal cancer comprises the use of radiotherapy where four main aspects have to be taken in consideration, not only by the surgeon, but also by the entire multidisciplinary treatment team (MDT-board).

The first aspect is the timing of treatment; namely, Pre- or Postoperative (Chemo)-Radiotherapy.

The other considerations if preoperative radiotherapy is used concern:

1. The waiting time from the end of the radiotherapy to the surgery
2. The use of a sphincter preserving surgical option and finally
3. Decision-making if the radiotherapy results in a complete response.

†Author was deceased at the time of publication.

Editor's Note:
This chapter by Professor Påhlman was commissioned at the start of this book project because of his integral involvement in the Swedish Rectal Cancer Trials initially utilizing short-course radiation therapy in all stages of disease. This practice and its outcome changed the world view towards preoperative treatment and resulted prior to the era of standardized surgery (TME) in a marked reduction in locoregional recurrence which was the principal problem with rectal cancer excision. It was one of the only trials to also demonstrate an improvement in cancer-specific survival. We invited Professor Påhlman to provide the surgeon's view on adjuvant radiotherapy in rectal cancer and upon its development as a concept in Sweden. Shortly after he submitted this work he died and we have left the chapter unedited reflecting the state of play in 2014 so that it may be compared with current standard practice. This book is dedicated to him and his lasting legacy.
Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336:980–7

J. Folkesson · Å. Collin · L. Påhlman (✉)
Department of Surgical Science, Uppsala University, Uppsala, Sweden
e-mail: joakim.folkesson@surgsci.uu.se; lars.pahlman@surgsci.uu.se

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Today's thorough preoperative investigations and the multitude of treatment options effectively leads to too many variables in the decision-making process for a single surgeon to handle. Therefore all these aspects must be evaluated and discussed in an MDT-board meeting which includes surgeons, medical and radiation oncologists, radiologists and pathologists [1]. All patients must be properly staged defining the local growth and the presence of distant spread prior to the commencement of treatment. The most important and crucial part of the local tumor staging is an accurate Magnetic Resonance Imaging (MRI) of the rectum.

Pre- Versus Postoperative Radiotherapy

There is overwhelming evidence from al large bank of data in the literature supporting preoperative over postoperative radiotherapy. In this regard, two large randomized trials (the Uppsala trial and the German trial), each with the specific aim of addressing this question showed that the local recurrence rate is less if preoperative radiotherapy is administered and that there is less acute toxicity of the radiotherapy treatment if is given preoperatively [2, 3]. In the Uppsala trial, preoperative short-course radiotherapy was tested against prolonged postoperative radiotherapy in locally advanced cancers, at that time designated as Dukes' B and C cases. The German trial tested preoperative- versus postoperative chemoradiotherapy. A large-scale meta-analysis performed on all randomised trials before the TME-era shows the same results; namely, that preoperative irradiation is better than postoperative radiotherapy [4]. Both the Uppsala and the German trials were running before MRI was considered the standard of care for staging but today it is clear that a preoperative staging based upon a good-quality MRI examination prior to surgery is mandatory in the decision-making process. In the Uppsala trial, the local staging was most often made on a clinical impression whereas in the German trial it was decided by a combination of clinical and/or ultra-sound staging. With an 'educated MRI staging' it is today possible to define those patients who require radiotherapy and to separate those cases where radiotherapy might be considered superfluous. In this calculation, the findings to consider include: the extent of tumour growth within the perirectal fat, the presence of lymph nodes within the mesorectum, demonstrated vascular invasion and the definition of lateral lymph nodes lying outside the surgical plane (of the mesorectal fascia). Moreover, it is important to delineate the distance to the mesorectal fascia itself in mid- to high rectal cancers and whether there is involvement of the pelvic floor or in low rectal cancer cases of the sphincters. The type and choice of radiation technique (short-course, long-course or concomitant chemotherapy) is discussed elsewhere in this section and in this book. The authors provide their philosophical insight into the use of RT from a surgical perspective.

Timing of Surgery After Preoperative Radiotherapy

Short-Course Radiation

Traditionally, after short-course radiotherapy [5×5 Gy over 1 week], once it was introduced, the recommendation was to operate immediately (the following week) after the end of the radiotherapy [5]. As a result of our protocol, in most trials testing the efficacy of preoperative short-course radiation, surgery was recommended in the beginning of the first week after radiotherapy. The main reason for this was that the acute toxicity to radiotherapy appears 2–3 weeks after irradiation and so as to avoid operating upon patients during that period, early surgery was proposed. Moreover, many surgeons at that time had the view that surgery should not be postponed for too long a period and were generally reluctant to add to surgical delays. This hesitation was actually the most important reason why the short-course treatment was able to be introduced into Sweden after our initial trials in Uppsala where it was adopted nationally.

Long-Course Radiation

Long-course radiotherapy (1.8–2 Gy daily in ≈25 fractions) was initially designed as a postoperative treatment. During this time, concomitant chemotherapy was also initiated and when data became evident that the treatment should be given preoperatively, the question of the timing of surgery was again part of the discussion. Since patients suffer acute toxicity (diarrhoea and sometimes leucopoenia) and are often not in an optimal shape for immediate surgery, delayed surgery was preferred. There was actually on this background, however, no real knowledge concerning the best timing of surgery, but empirically it was based upon the fact that most of the acute toxic reactions to radiation had subsided by 4 weeks. Consequently the recommendation was to operate upon patients after long-course (chemo)-radiation in 4–5 weeks after the end of the radiotherapy.

The Situation in 2014

No differences in the effect on local recurrence rates or survival between preoperative short-course and long-course radiotherapy have been reported. With the initial recommendation to operate after 4 weeks, more acute toxicity is seen with long-course irradiation, but if surgery after short-course irradiation is delayed, similar toxicity (diarrhoea and leucopoenia) is noted [6]. Moreover, no significant differences in postoperative morbidity or mortality have been detected between the two

treatment schedules, as tested in two randomised trials, one from Poland and one from Australia [7, 8]. An important observation is that there is no experience with concomitant chemotherapy and short-course radiotherapy whereas, this is the standard of care today with long-course radiotherapy.

Over the course of investigation, the timing of surgery following completed radiotherapy has progressively been delayed. This postponement has occurred, however, with only scant evidence. The knowledge we have today is mainly based upon series with complete responders and from wait-and-see schedules and it is evident that more patients will have complete responses if the surgery is postponed beyond 6 weeks [9]. With short-course radiotherapy this has been tested in a randomised fashion in the Stockholm III trial. In that 3-armed trial, patients were randomised to (1). Short-course irradiation and immediate surgery, (2). Short-course irradiation and delayed surgery (3). Long-course radiation alone and delayed surgery. The trial was closed in 2013 and the primary endpoint (local recurrence rate) will be reported in 2016. Preliminary data on toxicity do support the impression that there is a 'window' of 2–3 weeks following irradiation when surgery should not be performed [6]. This is in line with data from all old trials [10, 11] from our group and from The Netherlands. More precisely, postoperative mortality is increased if surgery is performed at the end of the week following irradiation or during the second week after irradiation [6, 11]. If the classic recommendation with short-course irradiation should be followed, the ideal setting is radiation Monday to Friday and surgery the following, Monday, Tuesday or Wednesday. If that schedule for various reasons cannot be followed, surgery should be postponed for at least 3–4 weeks.

What has also been shown in both arms with delayed surgery in the Stockholm III-trial is a down-sizing of the tumour as well as complete responders. With chemoradiotherapy there are more data, all currently somewhat anecdotal (in that there has been no randomization but only many hospital series) which have shown that up to 25–30% of the tumours will respond completely within an 8 to 12 week period [9, 12]. This effect is dependent upon the tumour size. If the patient is not planned to enter a 'wait-and-watch' program there is no rationale to wait that long for surgery and to potentially increase the risk of metastasis occurring during a prolonged wait [13]. Consequently, most guidelines today recommend surgery 4–6 weeks after completed long-course chemoradiotherapy. This time period is arbitrary and again there is no strong evidence to support this dogma. If short-course irradiation is used, guidelines still recommend immediate surgery the following week, although delayed surgery is used more often than not, mainly due to logistical reasons.

It has become evident that the standard of care is changing towards a postponement of surgery, although this is without any real strong supportive evidence. One reason for this strategy is to give the tumour a chance to shrink in order to make it possible to perform more sphincter preserving procedures. Another reason is the 'wait-and-watch' philosophy. The risk taken, when surgery is delayed, is that growth of micro-metastatic disease in the liver and the lungs is possible during this time period. Normally, adjuvant chemotherapy is delivered 4–5 weeks postoperatively, but if surgery is delayed up to 2 weeks, or as much as 3 months (including the recovery time from surgery), there is a real risk of repopulation of occult metastases to a

size or burden which is not curable with chemotherapy. Therefore, this modern trend can furnish a strong argument against this strategy, especially due to the fact that the patients who require radiation also have the highest risk of having occult metastases. New trials are ongoing, like the RAPIDO-trial, addressing this problem, but no data are available so far [14].

Sphincter Preservation

It has been shown in many hospital series that there are more sphincter preserving procedures being performed nowadays than before and many authors have claimed the down-sizing effect of radiotherapy to be responsible for this increase in sphincter preservation. However, the change in surgical attitude is probably more important than the down-sizing effect induced by radiotherapy. The dogmatic recommendation of a 5 cm distal margin of clearance has been challenged and there is ample data supporting the assertion that a 1 cm distal margin is sufficient in very low rectal cancer [15]. The 5 cm rule is only justified in high rectal cancer where a partial mesorectal excision (PME) is considered.

In many randomized trials comparing surgery and preoperative radiotherapy versus surgery alone, or preoperative radiotherapy versus postoperative radiotherapy, there are no general differences in the rates of sphincter preservation. In this regard, meta-analyses and raw data do not really support sphincter preservation as a consequence of neoadjuvant treatment [16, 17]. However, there are some problems with these analyses since most trials run according to an 'intention-to-treat' principle; where for example if the initial decision is that the patient requires an APR, then an APR should be performed despite any down-sizing effect. Based upon the new philosophies, however, there are now data that do support surgeons changing their initial treatment plans after a repeated evaluation before surgery and for the surgeon taking into consideration tumour shrinkage after preoperative (chemo)-radiation. Specifically, there is an increased chance that a sphincter preserving procedure can be used if the waiting time is long enough. In this respect, the subgroup analyses from the German trial comparing pre- versus postoperative chemoradiotherapy showed that in those centres where surgeons had an awareness of tumour down-sizing and could decide to change their treatment plan if there was such a response, the incidence of sphincter preservation was higher [3]. However, the ultimate randomized trial has not yet been conducted. There have been trials comparing short-course versus long-course chemoradiotherapy with the primary end-point of sphincter preservation but those trials have not been able to show any difference [7, 8].

There is still a debate and a difference in the thinking process based upon how patients are evaluated after radiotherapy and a prolonged waiting time. Probably a small number of patients will have a sphincter preserving procedure if the waiting time is successful and the tumour has down-sized sufficiently, but the most crucial end-point in such a setting, the risk of increasing the local recurrence rate with this

approach, has not been addressed in well performed randomised trials and there are no proper reports from existent clinical series. There is of course also the real risk in long waiting times of unmanageable metastatic disease.

Wait-and-Watch Program

In the changing world of rectal cancer treatment, when patients have been operated upon more than 6–8 weeks after the completion of radiotherapy, the final pathological examination has shown in some cases that the tumour has disappeared with a complete response either to radiotherapy alone, or in combination with chemotherapy [18]. With this observation in mind, and in analogy with the modern treatment of anal carcinoma, one can argue whether or not surgery is necessary in such a case. The first unit taking advantage of this observation was the Brazilian group headed by Angelita Habr-Gama who deliberately administered radiotherapy to low rectal cancers where an APR would normally be required. If the tumour disappeared after chemoradiotherapy (most often rather small tumours) then the surgery was postponed. In her preliminary series, approximately 25% of the patients who received chemoradiotherapy had not been operated on at all and have an acceptable to normal bowel function without surgery [12]. This concept has now been tested by several other groups and more data appears in literature showing that if the tumour is almost gone by 8 weeks, then the decision for surgery should be postponed for another 4 weeks [19–21]. At 12 weeks after radiotherapy the decision should be made whether or not the patient should be operated upon. If there is a clinical complete response at this time, data do support that it is comparatively safe to include such a patient into a “wait-and-watch” program with meticulous follow-up. Precisely how this follow-up schedule should be managed is not yet clear but by analogy with anal carcinoma, it is expected that the patient should be reviewed at least every second to third month during the first year, with endoscopic and digital examination. After the first two years of close follow-up, the interval can be prolonged. The use of both ^{18}FDG-PET-scanning [22] and MRI [23] during the follow-up is still under evaluation. For the time being the most important tools are rectal palpation and endoscopy since most data support the impression that tumour tends to recur first within the lumen.

Another interesting area which requires further investigation is what best to do when the tumour is almost gone but when there is still just a small residual remnant left in the rectum. How are these patients optimally treated? Should the surgery be performed with an abdominal radical procedure, (i.e. an anterior resection or an APR), or is a local excision, preferably with transanal endoscopic microsurgery (TEM), sufficient? Several trials are ongoing but one randomized trial has tested this hypothesis. In this Italian trial, patients with a cT2 or an early cT3 tumour received preoperative chemo-radiation. Depending upon the response to the chemo-radiotherapy patients were then enrolled to be randomised to either local excision with TEM or to a laparoscopic anterior resection or APR [24]. No difference

regarding survival or local recurrence was detected, although critique has been raised about this trial being seriously under-powered. Toxicity was less but the quality of life was better if just a local excision was performed when compared with an abdominal procedure. This scenario with rectal cancer responding completely or partially to radiotherapy is a relatively new concept and several trials or series are ongoing which are attempting to evaluate the use of local excision or just a "wait-and-watch" approach.

There is no randomized trial that has yet tested the "wait-and-watch" program with surgery and more than likely, such a trial will probably never be conducted. As for anal carcinomas, it has proven impossible to obtain informed consent to randomise patients to "wait-and-watch" or surgery with an APR and now this situation has become exactly the same for rectal cancer. The main question with the "wait-and-watch" program is whether or not all rectal cancer patients should be considered for this strategy. Perhaps only patients with a low tumour, where an APR is the expected option, should, however, currently be included in such a study. But what of patients with a tumour at 10–13 cm from the anal verge? Most surgeons clearly still believe that a high rectal cancer is best treated with an anterior resection since there is a high possibility of achieving local cure without the need radiotherapy, thereby avoiding the complications imposed by irradiation. As stated, the "wait-and-watch" program will most likely only be tested in low rectal cancers where the only alternative is an APR.

Other options for low tumours, either with primary radiotherapy or as an adjunct include brachytherapy and endocavitary contact irradiation, covered elsewhere in this section. In these settings, high doses of irradiation can be administered directly to the tumour with low toxicity and complete responses can often be achieved in selected cases [25, 26]. These responders are also followed-up in wait-and-watch programs, although so far, this approach has not been generally accepted. The more widespread a screening program becomes, the earlier the detected tumours, (especially those which are non-symptomatic). This will probably increase the demand for local treatments and may in the future expand new therapies which incorporate local management of responding rectal cancers.

Summary

The management of rectal cancer has changed dramatically over recent decades and is still in a state of flux. The role of irradiation is discussed mainly in the context of toxicity in combination with surgery. Irradiation clearly reduces the risk of local recurrence and induces tumour down-sizing, and when judged necessary, should be delivered preoperatively. The timing of surgery after irradiation and the change of philosophy towards more sphincter-preserving procedures are both still the subject of intense debate. The "wait-and-watch" program is still also considered somewhat experimental where more data are required to cement its indications and contraindications. By analogy with breast cancer, where there are more small tumours that are

found on screening, major surgical procedures might potentially be considered overkill with their attendant postoperative mortality (particularly in the elderly) and early and late morbidity.

Editor's Note The outcome data of the Stockholm III trial are discussed in the commentary to this chapter (Chap. 20). The issue of a selective "wait and watch" policy towards rectal cancer is discussed in Chap. 11 of Part IV.

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Chapter 19
The Swedish Approach

Bengt Glimelius

Introduction

Rectal cancer therapy has in Sweden been individualized for decades, basically preempting current therapy. The tools to allow such individualized tailoring have, however, substantially been improved. Therapeutic decisions should be made by a multidisciplinary team prior to any therapy requiring patient-specific information, delineating the relevant data concerning tumor extension by magnetic resonance imaging (MRI) and correlative tumor pathology. The competence of the team, recorded as its "track-record" following quality registration is an important benchmark reflecting the volume of rectal cancer cases managed and the implementation of established management protocols. For the majority of primary rectal cancers, the choices include:

1. Direct surgery where the risk of local failure is so low that a further decrease in incidence afforded by preoperative radiotherapy would not be meaningful considering its toxicity and costs. This consideration is made for early or 'good' tumors which constitute between 20% and 30% cases overall
2. Preoperative short-course radiotherapy followed by immediate surgery. In this instance, the presumptive risk of local failure is deemed too high and would be decreased by 50–70%. This is considered an intermediate or 'bad' group of patients representing in different referral bases between 30–40% of referred cases
3. Preoperative chemoradiotherapy with a delay before surgery in order to allow downstaging/tumor downsizing. This is considered for the locally advanced, so-called 'ugly' group which might represent a 25–30% referral base. In this latter

B. Glimelius (✉)
Department of Immunology, Genetics and Pathology, Uppsala University, University Hospital, Uppsala, Sweden
e-mail: bengt.glimelius@igp.uu.se

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group, short-course radiotherapy with a delay is a worthy option in the elderly case and in those patients with significant co-morbidity.

Definitive radiotherapy or chemoradiotherapy used for organ preservation may be valuable in selected patients with early tumors where dose-escalation as a peripheral boost is employed for very advanced tumors (1–2% of all cases in general). The outcomes in Sweden have been substantially improved during the past decades utilizing this selective approach.

Background

Some decades ago, it was noted that a substantial proportion of patients who underwent radical surgery for rectal cancer severely suffered from the problem of local recurrence and that hospital beds in general surgical departments were frequently occupied by these patients with prolonged length of hospital stay. In this regard, retrospective analyses reported that an average of 38% of the patients at several hospitals in middle Sweden had a local failure [1]. This high figure together with the severe short-term suffering of patients combined with the limited or only temporary benefit of surgery and external beam radiotherapy, were principal factors in leading to studies which deliberately explored the value of radiotherapy (RT) in addition to surgery where the aim was clearly to lower the rates of locoregional recurrence.

Concerning this point, postoperative RT alone or sometimes in combination with 5-fluorouracil (FU, CRT) had been extensively tried in those patients with an unfavorable pathology and particularly in cases where the surgery had been considered to be of a questionable radicality. In this setting, historically, the experience proved fairly unfavorable in terms of local control of disease. Early on, there was also a wider belief amongst radiation oncologists that preoperative (C)RT might be more effective and better tolerated than the same therapy used postoperatively. This prevailing view was subsequently confirmed over the ensuing decades in studies comparing the cancer-specific outcomes between pre- and postoperative RT courses in higher risk rectal cancer cases [2–5].

Schedules were designed so that surgery which was deemed the most important component of rectal cancer therapy was not delayed. This led to the implementation of a highly fractionated schedule, administered during one week with surgery conducted the following week; a schedule protocol designed and clinically tested in Uppsala in a phase II study which was initiated late in 1977. The experiences of our group with the 5 × 5 Gy (initially 5.1 Gy) schedule corresponding to a total dose of 46 Gy in 2 Gy fractions was, according to the knowledge then available, very favorable [6]. This has led to a series of large randomized phase III trials, initially in Sweden but later conducted elsewhere, which have proven the efficacy of this preoperative approach in lowering cancer failure rates [2, 7–13]. The tolerability by patients in these mixed trials has generally been “excellent”, although this was not the case in one of our studies where a suboptimal radiation technique was used [9].

As one of our first reports, although the LR rate was reduced in the preoperative RT group there was no observable difference in the frequency of distant disease or overall survival. Those locally recurrent cases experienced a delay in their recurrence time but also experience a higher postoperative morbidity and mortality. This "short-course" preoperative schedule, however, became a reference treatment for many countries worldwide in application to subgroups of rectal cancer patients. This chapter describes the basis behind the present recommendations for preoperative RT (or CRT) in Sweden.

The "Good-Bad-Ugly" Concept

Rectal cancers may present as a spectrum ranging from minute cancers detected during microscopic evaluation of a rectal polyp to large infiltrating locally advanced tumors extensively invading surrounding tissues or organs. It is obvious that these markedly differing clinical presentations require different treatment strategies in order to optimize outcome. This is by no way unique for rectal cancers and the principles apply to most other cancers. At the time of diagnosis, most rectal cancers are free of detectable distant metastasis, but some 20–25% are metastatic on presentation. Patient-related factors including even their cultural aspects remain important with a great bearing on the choice of rectal cancer therapy.

In Sweden, rectal adenocarcinomas have for decades been discussed in three major clinical groups; namely, early, intermediate and locally advanced. This basic grouping differs from that used during the past two or so decades in many other countries, where basically only two clinical groups are typically described; namely, early and locally advanced. The rationale behind the three group approach has, however been incorporated into recent European guidelines [14–17] and into individual countries [18, 19].

Surgery is the most important curative treatment modality in rectal cancer. A tumor is presently considered as *early*, (or an alternative term frequently used in daily practice in Sweden is "good") if surgery can easily be performed with a resultant R0 resection (via standard total mesorectal excision – TME) where it is anticipated that there would be a very low risk of local failure (at the most 2–3%). An *Intermediate* or "bad" tumor can also immediately be operated upon with the expectation of an R0 resection and without the need for resection of adjacent structures/organs, however, the risk of local failure in this group would not be negligible. In order to result in low local recurrence rates, additional RT, preferably used preoperatively, has proven efficacy reducing the risk of LR by 50–70% as reported in many trials [8, 10, 13, 20–22]. A *locally advanced* or "ugly" tumor cannot easily be operated upon with an R0 resection unless the patient undergoes an extensive and sometimes even multilating surgery with the removal of adjacent structures/organs. The issue of multivisceral resection is covered elsewhere in this book (Chap. 16, Part IV).

In order to achieve an R0 resection with low local failure rates, preoperative RT is mandatory. This treatment should then not only sterilize the peripheral tumor cells not easily removed, and which cause local failure, but also should result in sufficient down-sizing/staging which facilitates standardized radical surgery. Since the effects on tumor size by RT are not rapid [23–25], but may take weeks to months, a time interval between the start (or end) of the RT is required. This is not required in tumors considered to be "bad" but not "ugly".

In the past, terminology in Sweden of rectal cancer was confusing with the terms early, intermediate and locally advanced not being used. This early 'Swedish' approach then described many tumors as polypoid cancers, resectable and non-resectable. The terms tethered or borderline resectable were also used in some institutions for those intermediate tumors which were positioned between resectable and non-resectable cancers, with the group sometimes referred to generically as the non-resectable group. The distinction into different groups was previously made clinically just with digital examination ("the educated bio-probe") or with the aid of the rectoscope. This distinction was not very precise and entirely investigator-dependent. Presently, high resolution magnetic resonance imaging (MRI) offers resolution precision and identifies tumor growth extensions that allow a separation into the three groups as defined [26, 27].

Despite this historical view and its caveats, there is no international consensus about how to define the terms "early, intermediate and locally advanced" or "good, bad and ugly" as we have defined it, let alone how these terms might be clinically used or useful. In the original publications from the Royal Marsden Hospital London, the good and ugly tumors were defined as we have above whereas those tumors considered to be bad were cases where there was a high risk of distant but not local failure [28]. This area has been defined with the standardization of the TME procedure to focus on locoregional risks and has been supplemented by preoperative MRI to delineate those higher-risk cases where neoadjuvant therapy can support both a TME and in some cases sphincter preservation. Tumor characteristics indicating high-risk of local failure or systemic failure do, however, overlap so that a high-risk of failing locally usually also implies that there is a high-risk of pre-existent tumor dissemination (systemic failure risk). Other characteristics such as extramural vascular invasion (EMVI), which can be readily identified on MRI [29] do not necessarily, however, equate with a level of operative difficulty or for the need for neoadjuvant chemoradiation in their own right, but rather are signals of a more aggressive tumor type with a greater likelihood of the development of distant metastases [30, 31]. This is also true of other tumor characteristics more indicative of systemic rather than local relapse risk, such as the presence of multiple metastatic nodes (cN2), unless they are threatening the mesorectal fascia (MRF).

The terminology used in the present ESMO guidelines [15] has been that used for our rectal tumor descriptions ('good, bad, ugly') and in the definition of risk-adapted treatment as well as to define those patients best suited for postoperative therapy.

The term "locally advanced" rectal cancer has been used extensively in reports of clinical trials during the past roughly two decades as well as in many ongoing

trials (see www.ClinicalTrials.gov). This term corresponds to the "bad and ugly" groups, as defined above. Designating both intermediate and locally advanced tumors as all "locally advanced," however, does not separate tumors according to whether a delay between the preoperative treatment and surgery (during which tumor regression may occur) is required.

Subgrouping of primary tumors should be based upon appropriate staging and in accordance with the UICC (Union Internationale Contre le Cancer) [32]. In rectal cancer, staging is primarily conducted with MRI, with the possibility of correctly defining clinical T (cT) stage and with superiority over endoscopic ultrasound (EUS) in the evaluation of the relationship to the mesorectal fascia. The N-staging remains relatively less accurate using any of the imaging modalities [33] partly because up to one-third of nodal metastases are <5 mm in maximal diameter [34] and because a quarter of perirectal nodes are <5 mm in size [35]. The T- and the N-stage together with tumor height (as measured in cm from the anal verge) are, however, not sufficient to choose the individualized primary intervention for a newly diagnosed rectal cancer.

Treatment Principles in Sweden

Any staging system should be accurate, reproducible and immediately decisive for risk-based action. In rectal cancer, in Sweden these include direct surgery (a local procedure or most often a major resection), preoperative RT to decrease the risk of local failure but without the need for downsizing/downstaging and preoperative treatment with a delay (RT or most often CRT as this is slightly more efficient as a downstaging treatment) [36–39]. These three major options correspond to the "good", "bad", and "ugly" tumors, as described above. More recently, the concept of organ preservation [40] has added a new dimension, namely with the omission of surgery altogether when the clinical response to the (C)RT is complete (cCR). This 'watch and wait' policy is discussed in greater detail elsewhere in this book (Chaps. 11 and 12, Part IV).

The UICC TN-staging is as stated above, not sufficient to determine the appropriate treatment. Substaging of cT3 according to the depth of infiltration beyond the muscularis propria (a <1 mm; b 1–5 mm; c 5–15 mm; d >15 mm) adds relevant prognostic information, although this area has not yet been extensively studied [41, 42]. Equally, the presence of EMVI reveals that the risk of recurrence is higher, at least systemically and likely locally as well [29]. Finding that the tumor, or a pathological lymph node, threatens (<1 mm) or invades the MRF (0 mm or growth outside MRF or the corresponding anatomical structure), adds relevant information to the case, usually denoting that the tumor should be considered "ugly" and that the patient requires preoperative CRT. If the MRF-positivity is denoted anteriorly above the peritoneal reflection, thus affecting the peritoneum as a cT4a tumor, there is also a high risk of failure, although this sort of tumor does not require to be downsized/downstaged prior to surgery. Similarly, a threat to the fascia at the level of the leva-

tor muscles or in the MRF anteriorly towards the vagina or uterus also means that there is a high risk of local failure, but not necessarily that the case needs specific downsizing/downstaging. In this instance, the onus is more on technically appropriate radical surgery being performed (namely, an extra levator dissection or resection of the dorsal vaginal wall/uterus, respectively).

The anatomical tumor extensions described in the preceding paragraph can be evaluated on MRI and thus effectively incorporated into a clinical staging system. Of relevance for the choice of therapy is also the measurable distance from the distal part of the tumor to the anal verge or to the pelvic floor. The size/bulk of the mesorectum varies between the sexes and amongst individuals so that in every individual case the orientation of the rectal lesion bears a relationship with the direction and the distance from the anus and the peritoneal reflection. In this sense, it is comparatively difficult to incorporate all of these measurable parameters in a simple way into a staging system. Another variable in management is the experience and outcome of a multidisciplinary rectal cancer group. Although there is an accreditation process for the radiologist and also the surgeon, there is little standardization for medical oncology, so that the "track record" of the team is the best way to judge overall MDT competence, requiring some sort of quality control of all the relevant aspects of care. The surgeon for example has the opportunity to evaluate the resected specimen where the pathologist can make an objective assessment of the TME as part of a standardized quality control [43]. Complete follow-up with registration in a "quality registry" is also required in order to evaluate the competence of the entire team [44]. If a local failure has been recorded, a thorough examination of all details in the care will provide further insight, explaining the purported reasons for LR on a background of acceptable and comparable standards [45].

The main aspect of the "good, bad and ugly" concept is to introduce a new way of thinking, resulting in the most appropriate choice of therapy. This view is principally based upon the stage (TN, T3 substage, presence of EMVI, MRF-status), however, it incorporates patient-related, anatomical factors and the track-record of the management team. The recommendation of the multidisciplinary team (MDT), afterwards to be presented and discussed with the patient, can then proceed as:

1. Either operation directly, as the risk of local failure is so low that further reduction by preoperative RT is not triggered. This situation may apply even if RT provides a big reduction in risk since the overall risk of LR is deemed very low (e.g. If RT reduced LR by about 70%, but if the raw numbers went from for example 4% down to 1%)
2. Administer preoperative RT with immediate surgery since the risk of a local failure is too high (e.g. 8–10% or more)
3. Downsizing/downstaging is required since the probability of an R0-resection is not very high (>99%).

This type of approach is one step towards personalized medicine, however, it is not strictly based on the tumor biology which is a more usual feature of what we

mean by "personalized medicine" for example in the use of targeted therapies. From the above discussion, it follows that a defined stage, according to the TNM-system, even if complemented with other tumor-related parameters not yet incorporated into UICC TNM, is insufficient to guide therapeutic decision-making. It would seem intuitive that any staging system cannot incorporate patient-related factors in specialized higher-risk states, such as advanced age, the presence of severe co-morbidities and patient choice. Each of these states has the potential to deviate from standard or accepted practice. Difficulties within such protocols are more reflective of variations within the tumor than within the patient, such as those features describing tumor extension into anatomical landmarks. The more complex the system the harder it is going to be to regularly use it, and also to audit, so that simpler systems may need to cherry pick the most important parameters as defined by retrospective multivariate analysis and then prospectively validate their utility. This cumbersome work incorporating the MDT has yet to be done.

What TN-Subgroups Are Included in the Three "Therapeutic" Groups?

Although no definitive answer can be provided, for certain TN-substages, it is easier to refer them to a specific subgroup, whereas for others, a grey-zone exists. Algorithms have been produced and published [15, 18, 46], all stating in footnotes that other parameters are equally relevant. A slightly modified variant of the algorithm to be incorporated in the coming Swedish Care Programme and can be found at: (http://www.cancercentrum.se/sv/Kvalitetsregister/Kolorektalcancer/Rapporter) Data from this group is shown in Fig. 19.1. Any modifications can ultimately be made where the recommendations of a specific therapy are partly driven by inclusion criteria in ongoing clinical trials. It should be further noted that there is no international consensus concerning which TN-subgroup to include within any specific management group (i.e. Groups I–III). The Dutch group (Maastricht University Medical Center) and also NICE, UK [18, 19] have followed similar algorithms as this one used in Sweden where the different therapeutic options including surgery, are developing, further adding to the view as stated that "subgrouping is a moving target".

An anatomically defined staging system is still required allowing comparisons between institutions and which will be flexible to incorporate future defined parameters. The clinical TNM-staging, presently in accordance with the 7th edition of 2010 [32] should be used although the TNM-systems must continuously be developed so as to incorporate new knowledge. These systems cannot, however, be changed too frequently and they require international consensus permitting comparisons with historical patient series. The changes made for example between

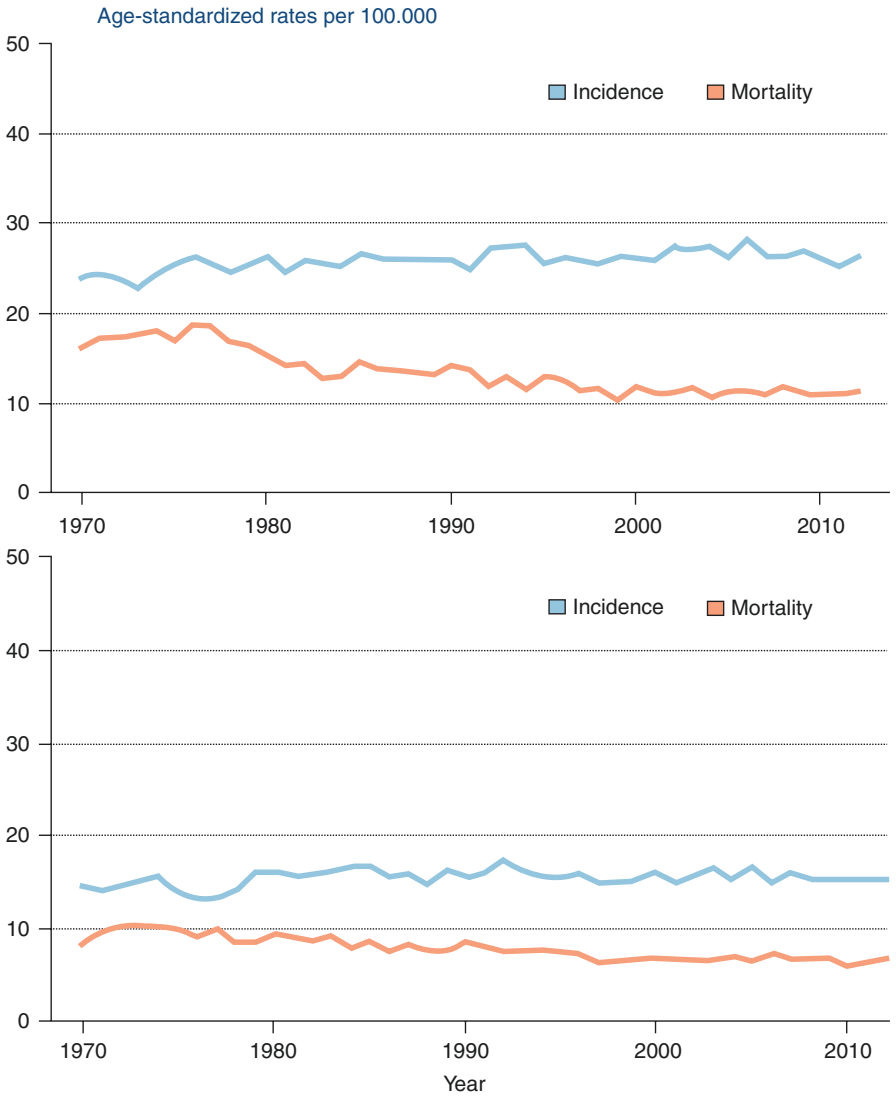

Fig. 19.1 Decreasing age-standardized mortality rates and slightly increasing incidence rates of rectal cancer in Sweden since the 1970s. (Males above and females below). The figures are taken from the 2013 annual report of the Swedish Colorectal Cancer Registry (http://www.cancercentrum.se/sv/Kvalitetsregister/Kolorektalcancer/Rapporter)

TNM5, TNM6 and TNM7 for rectal cancer have been criticized partly for these reasons [47]. As an anatomical staging system for rectal cancer TNM7 is already insufficient. The subdivision of cT3 (a-d), the presence of EMVI and the relations of the tumor to the MRF are all as already stated highly relevant, but within the system require some fine-tuning before they are fully incorporated into a TNM8 scheme.

The Need for More Than Three "Therapeutic" Groups

Since surgery alone can be either a local procedure or a conventional major resection, a selection of these options must also be made. As the local procedures, like the transanal endoscopic microdissection (TEMS), do not remove the draining lymph nodes, for this approach the risk of lymph node metastases must be very low (≤10%). This issue is covered elsewhere in this book (Chap. 9, Part IV). The cT2N0 tumors are not primarily of interest for a local procedure, whereas cT1N0 tumors are suitable. However, the risk of lymph node metastases differs within T1-tumors which are an eclectic group so that only those which have limited submucosal extension (the pT1sm1, but potentially also the sm2, but not the sm3 tumor types) have a low risk of being N+ [48–50]. A pT1sm1(2) tumor belongs to a "very early" group and is presently separated from the conventional early group [51, 52]. In one recent study by Debove et al. [52] the risk of LN metastases was greater with morphological features (such as high tumor budding rather than the depth of submucosal infiltration). This would contradict the original work of Kikuchi categorizing submucosal involvement who found no LN metastases in their cohort of 35 patients with a pT1-Sm1 rectal cancer [53].

EUS is better than MRI in separating T1- from T2-tumors [54]. Additional RT (or CRT), again preferably preoperatively can eradicate microscopic tumor cells in the nodes, although major surgery has a higher probability of locally controlling tumor growth than postoperative CRT after a local procedure. Preoperative CRT for early tumors can limit (or defer) subsequent surgery and is discussed below in the section on organ preservation.

At the other extreme, some locally advanced tumors (ugly, cT4b) may be so advanced that surgery will likely never be sufficiently radical, even after conventional CRT up to a dose of 50–54 Gy and unless multilating surgery such as a pelvic exenteration is performed. We have tentatively named these tumors "ugly-ugly" where they require even higher radiation doses in order to sterilize the tumor cells more safely. A peripheral concomitant radiation boost with modern RT, using proton therapy for example [55] may be indicated in this very advanced group.

Organ Preservation

The response to RT, alone or with chemotherapy (CRT), differs markedly between tumors. In many cultures, there is a desire to avoid surgery at all costs, particularly if it may result in a stoma or in a disabling low anterior resection syndrome (LARS); both in tumors where the patient might receive CRT. Attempts to avoid or limit surgery in unfit patients (e.g. the very elderly or the severely co-morbid case) is part of traditional Swedish practice using as high a radiation dose as is possible, frequently in combination with concomitant 5-FU. No systematic analyses of the Swedish results have been conducted and published, although our experience is similar to that recently reported from Poland [56]. Radu et al. [57] retrospectively

evaluated the experience of a short-course 5 × 5 Gy schedule with a delay in patients not fit for CRT and found a good tolerability and tumor control in most patients so treated. Similar results have been reported from our Stockholm group [58] and also from the UK [59] combining low toxicity with some downstaging in these high-risk patients. These results together with results from randomized trials support our notion that the cell kill effect from 5 × 5 Gy is the same as that from CRT up to about 50 Gy, and superior to 50 Gy RT alone [11, 12, 32, 60].

Organ preservation in the sense that it is presently practiced, (viz. the avoidance or limitation of surgery in fit patients with tumors responding very well or completely to CRT) [36, 61–63] has by contrast, not been frequently practiced in Sweden. There are probably many reasons for this situation, part of which is the historical and philosophical approach towards CRT in the country. Firstly, a stoma in Sweden generally is not considered to be the same 'trauma' as it perhaps may be in some other cultures or environments. Secondly, CRT has only been used in the locally advanced, "ugly" tumors rather than as a test for completely responding earlier cancers. These latter 'ugly' cases are usually large and with the present therapy of about 50 Gy combined with a fluoropyrimidine as a radiosensitizer so that they are not very suitable cases for organ preservation. Clinical complete responders (cCR) and also pathological complete remissions (pCR) are seen in about 10–15% in this population, although it is currently uncertain whether the cCRs in this group are durable [64]. The default management of the smaller tumors usually results in local surgery, whereas the intermediate larger cancers tend to undergo short-course preoperative RT followed by definitive surgery without a current National strategy of organ preservation. In Sweden now, organ preservation should be considered in those cases with a cCR after CRT, as well as in patients who would otherwise be candidates for upfront surgery or for 5 × 5 Gy with immediate surgery. For the group of patients who are most optimal for organ preservation, the options include direct surgery with its attendant morbidity, or CRT with approximately a 30% chance of a cCR and a 20% chance of avoiding surgery altogether. Even though it is possible that the long-term survival could be similar, the added morbidity for most patients is seldom considered.

In an effort to increase the possibility of organ preservation in early cancer (cT2-early T3 <3–4 cm), there are Swedish units which have sufficient experience and equipment to boost RT with brachytherapy or endoluminal contact therapy [65]. We are planning participation in the coming international randomized trial (OPERA) where the value of a local boost with contact therapy will be explored (JP Gerard, Nice, France, pers. communication; NCT02505750). This trial is designed to assess the safety of a boost (Endocavitary Radiation Therapy With Contact X-ray Brachytherapy [CXB] or EBRT) in combination with neoadjuvant chemoradiotherapy for early rectal adenocarcinoma (cT2, cT3a-b tumors <5 cm) with EBRT (9 Gy/5 fractions) or CXB (90 Gy/3 fractions) and with the endpoint of organ preservation at 3 years in the absence of non-salvageable local pelvic recurrence (Table 19.1).

Integrating Radiotherapy and Chemotherapy to Improve Survival

The markedly reduced risk of a local failure (presently 4% in the entire Swedish population; *vide infra*) has not been accompanied by the same marked survival improvement. However, it is wrong to state that survival has not improved as it has from about 40% after 5 years in the 1960s to 50% in the 1980s and to above 60% after 2000. Since the efficacy of adjuvant chemotherapy in rectal cancer is limited, at least after preoperative (C)RT, [66, 67] the hypothesis that neo-adjuvant chemotherapy will kill a higher proportion of the subclinical metastases (which ultimately kills the majority of the patients who will die from rectal cancer), resulted in the randomized RAPIDO (**R**adiotherapy **A**nd **P**reoperative **I**nduction Therapy Followed By **D**edicated **O**peration; NCT 01558921) trial [68]. In the trial, only including patients at high risk for local or systemic failure (i.e. all ugly tumors and bad tumors with MRF+, EMVI + or cN2), patients are randomized between a reference treatment, CRT to 50–50.4 Gy with capecitabine, surgery and optional adjuvant 8 cycles with capecitabine-oxaliplatin (CAPOX) or to short-course RT, 6 cycles of neo-adjuvant CAPOX and surgery. Centers from about 8 countries are participating, with the inclusion of almost 500/840 patients by late 2014 (www.dccg.nl/trials/rapido).

Table 19.1 Indications for preoperative treatment in rectal cancer based upon the risk of local recurrence

Distance from the anal verge	cT1–2 mrf-	cT3ab mrf-	cT3cd mrf-	cT3 mrf+ cT4a/b	N1 mrf-	N2 mrf-	LN+	EMVI+ mrf-
	N0	**N0**	**N0**	**N0**				
10–15 cm	0	0	0/5 × 5	5 × 5/CRT	0/5 × 5	5 × 5/CRT	CRT	5 × 5
5–10 cm	0	0/5 × 5	5 × 5	5 × 5/CRT	5 × 5	5 × 5/CRT	CRT	5 × 5/CRT
0–5 cm	0/5 × 5	5 × 5	5 × 5	CRT	5 × 5	CRT	CRT	CRT

T1: invasion into submucosa, T2: invasion into muscularis propria, T3: invasion outside muscularis propria (cT3a: <1 mm, cT3b: 1–5 mm, cT3c: 5–15 mm, cT3d: >15 m, cT4a: peritoneal involvement, cT4b: overgrowth to other organs, cN1: metastasis in 1–3 perirectal nodes, cN2: >3 nodes). To be classified as N+, at least two of three malignancy criteria, size >5 mm, shape and structure, mrf+: mesorectal fascia is engaged <1 mm, LN+; pathologic lateral nodes outside mrf, at least 2/3 criteria (size >10 mm)

0 = no preoperative treatment, surgery directly

5 × 5 = preoperative short-course RT 5 × 5 Gy, direct surgery

0/5 × 5 = individual evaluation depending upon the estimated risk of local failure

CRT = preoperative chemoradiotherapy 25–28 × 2–1.8 Gy + capecitabine with delayed surgery. An alternative is 5 × 5 Gy with delayed surgery in patients who do not tolerate CRT

5 × 5/CRT = individual evaluation depending upon whether a delay before surgery is needed

Have Patient Outcomes Been Improved in Sweden?

In 1995, a nation-wide quality registration of relevant parameters on all rectal cancer patients in Sweden was initiated. It was preceded by multidisciplinary workshops where details of potential importance for outcome were dealt with. These workshops have continued along the lines developed in Stockholm [69]. The quality registration is close to 100% complete [45].

The improvements seen in Sweden prior to 1995 were likely quite marked, but have been scantily documented [70–73]. It is noted that the 5-year overall survival was better for rectal cancer than for colon cancer between 1985 and 1989 in the Uppsala county, where specific efforts to improve rectal cancer care started around 1980 when compared with the rest of Sweden [70]. A better overall 5-year survival for rectal cancer had not been reported before, but has over time now been demonstrated for the entire Swedish nation with the regularized introduction of TME [71]. Advantage has also been shown in other countries (such as the Netherlands and Norway) which have examined the outcomes during different time periods after the introduction of National rectal cancer management guidelines [74–76]. The improvements since 1995 have, when the first report from the quality registration was published, been documented annually since 1999 with analysis of the reasons behind such improvements. (http://www.cancercentrum.se/sv/Kvalitetsregister/Kolorektalcancer/Rapporter).

The ultimate outcome target of all social and health care-related activities against a specific disease is a reduction of disease mortality. In rectal cancer, the mortality has decreased, even if the incidence has increased (Fig. 19.1). The overall and relative survival patterns (Fig. 19.2) have improved during the past 15 years, as they also did during the preceding decades [70, 71]. Screening of healthy individuals for CRC has not been conducted in Sweden until about 2010 when it started in 1/6 health care regions. Local recurrence rates have also continuously decreased since the start of the registration (Fig. 19.3) where in the 1970s until the early 1980s it averaged 38% [1]. One aim has been to reach LR rates in the entire unselected population <5% after 5 years in both the preoperatively irradiated and the non-irradiated patients, without decreasing the proportion of patients undergoing resection. This aim has been reached, although the rate for some years remains slightly too high for those selected for primary surgery. Postoperative CRT is rarely administered (<1%). During the same time period, the proportion of patients irradiated has increased for tumors at all levels above the anal verge (Fig. 19.4). This increase has continued during recent years, in spite of the recognition that additional RT and CRT adds to the morbidity associated with surgery [77, 78]. The argument that the use of preoperative RT should be decreased (i.e. that the rate of overtreatment is excessive), has repeatedly been raised, but with little effect on RT utilization. If “organ preservation” will become popular in Sweden, the use of (C)RT will certainly increase as early tumors will be irradiated upfront.

The majority of all types of irradiation for rectal cancer throughout Sweden is with the short-course schedule following the recommendations that in most rectal

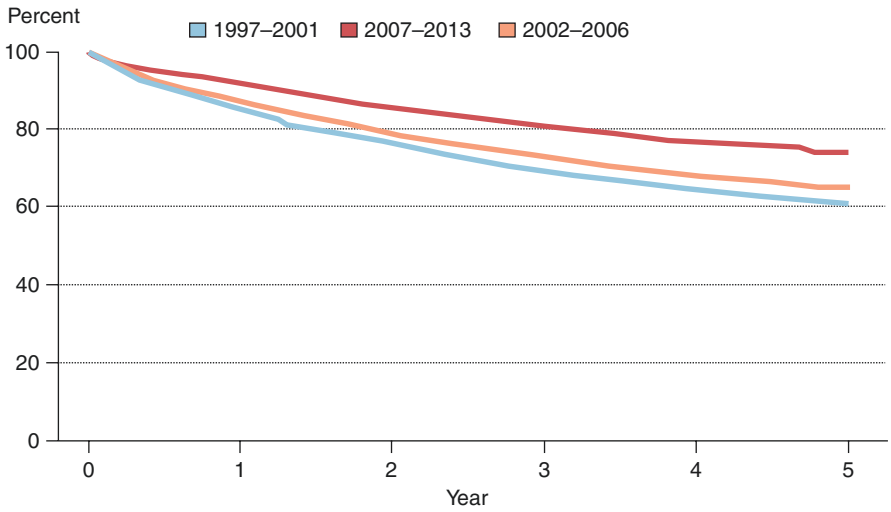

Fig. 19.2 Improved relative survival with time of rectal cancer in Sweden as seen in the Swedish Colorectal Cancer Registry

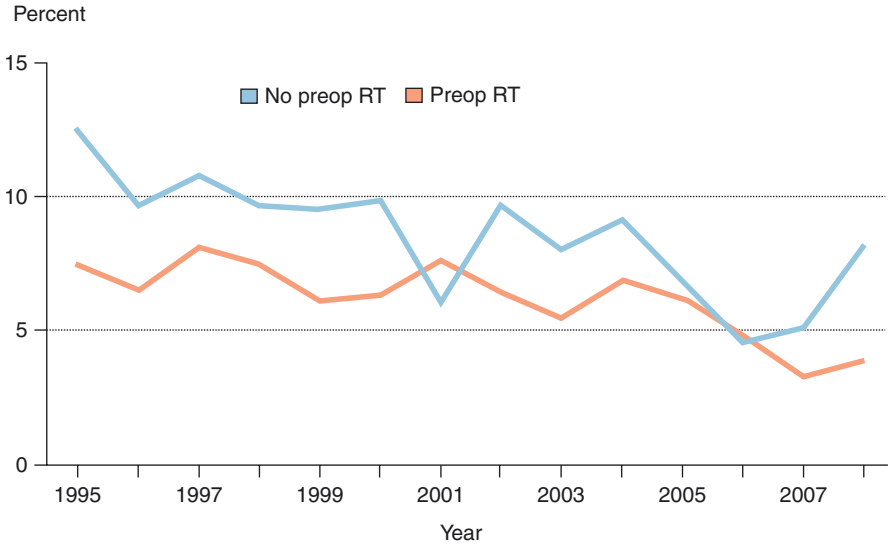

Fig. 19.3 Decreasing 5-year local recurrence rates in resected rectal cancer patients selected to receive preoperative (C)RT. Data from the entire Swedish population of patients undergoing an abdomino-perineal resection (APR), an anterior resection (AR), a Hartmann's procedure (HA) or a local excision (LE), irrespective of clearance outcome (including R0-R2 resections). In 2008, the local recurrence rates were 4% following an APR or an AR and 6–7% after a HA or a LE when both non-irradiated and irradiated patients were grouped together (*data not shown*). Swedish Colorectal Cancer Registry Report 2013

cancers there is no need for downstaging/sizing. In the 'ugly' 10–15% of tumors, long-course RT is routinely administered. This treatment has been implemented since around 2005, when information from randomized trials revealed that the addition of chemotherapy improved the local control [36–38]. The use of combined RT and chemotherapy has continued to increase during recent years in all health care regions except one (Fig. 19.5) and this is likely driven by the ongoing RAPIDO trial [68] which also includes patients with "bad" tumors at high-risk for systemic failure. In this trial, preoperative treatment in the control arm is CRT with a delay even if no downstaging/sizing is needed for many of the tumors registered in this arm. The growing trend to prolong the interval between RT and surgery (a trend which is not yet scientifically established) will also impact the statistics of RT use throughout Sweden [25].

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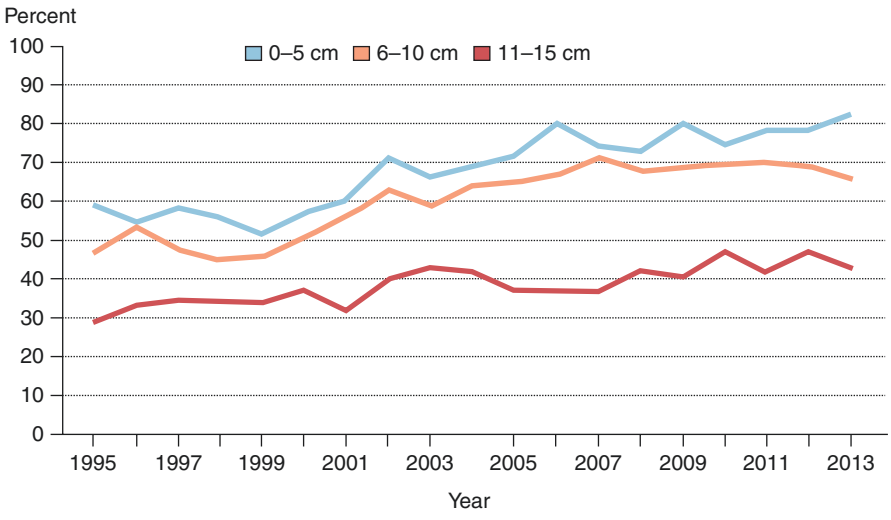

Fig. 19.4 Proportion of irradiated patients with rectal cancer according to the tumor level from the anal verge. (Data from the Swedish Colorectal Cancer Registry, 2013)

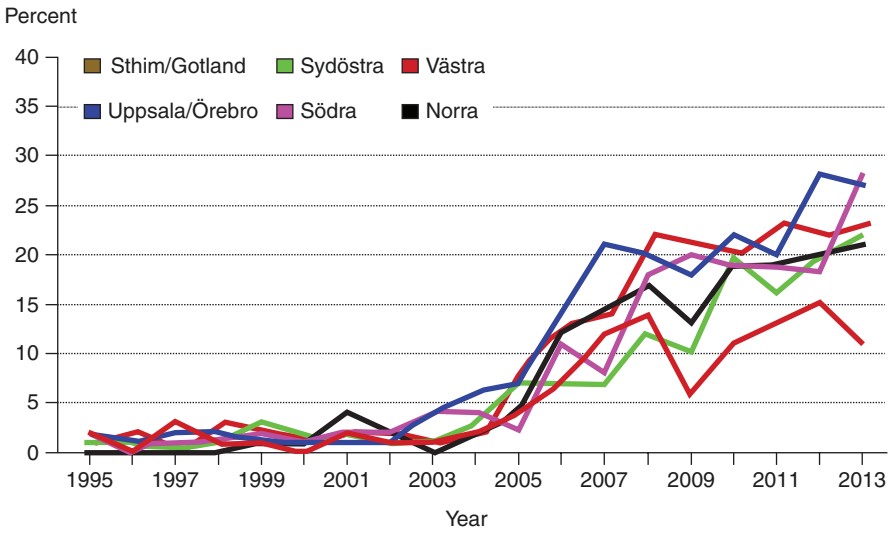

Fig. 19.5 A substantial increase in the proportion of patients in the six Swedish Health Care Regions receiving both radiotherapy and chemotherapy rather than radiotherapy alone preoperatively, starting about 2005 after the release of improved local control using CRT instead of RT alone (based on 3 randomized trials; References [36–38]). (Data from the Swedish Colorectal Cancer Registry, 2013)

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Chapter 20
The Swedish Approach Towards Radiotherapy and Rectal Cancer: Making Sense of Where They Have Been and Where They Are Going

Andrew P. Zbar

In this section I offer a personal view on what the surgeon should consider concerning data from radiotherapy (RT) trials in rectal cancer and particularly on the chronological development and meaning of the important Swedish RT data. Professor Påhlman's chapter was the first chapter delivered to our editors for this book on 20th March 2014 even when it was still a germinating idea. Lars Påhlman subsequently died from metastatic cancer at his Uppsala home on 21st November 2015. We have deliberately kept the chapter unmodified to provide some insight not only into his thinking concerning rectal cancer management but also to highlight his impressions back in 2014 of where the future might take rectal cancer care. It is not surprising that Lars was prophetic in his interpretation of the potential place of the "watch and wait" treatment initiated by Professor Angelita Habr-Gama. Improvements in radiation scheduling and chemotherapy combinations as well as in the imaging and the pathologic interpretation of tumour responsiveness are securing an expanded role for this approach in our patients with the deliberate presentation of both an Australasian and a North American perspective in this section and elsewhere in this book.

Although we have come to accept as routine the use of short-course radiotherapy (RT) followed by almost immediate surgery in some rectal cancers and also the idea of image-guided decision-making in a multidisciplinary team with prolonged neoadjuvant chemoradiation followed by surgery for more advanced tumors, these treatments didn't come from nowhere. We can sometimes forget the painstaking trialing that lay behind these protocols and can certainly forget or not even know the characters within coloproctology and beyond whose understanding of tumour biology drove these seminal trials. Lars Påhlman was certainly one of these farsighted gentlemen. Recently, even the short course RT approach has been modified with a delay in surgery [1] which appears on randomized trialing to substantially reduce the post-TME complication rate. In this commentary I wish to rekindle an

A. P. Zbar (✉)
University of Melbourne, Melbourne, VIC, Australia

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understanding of where we are now with RT and chemotherapy (CT) in rectal cancer management by an appreciation of where we have been.

The use of some form of preoperative RT has become the standard for many patients with rectal cancer. This is most typically delivered in one of two ways; either as a short course (25 Gy delivered in 5 Gy fractions over 1 week) or as long-course treatment (typically 50.4 Gy in 1.8 Gy fractions delivered over 5.5 weeks with concomitant 5FU-based CT). With the short-course RT, surgery is still most commonly performed within a week of the cessation of treatment but with the long-course treatment surgery is delayed for 4–8 weeks after the CT is complete. These RT delivery systems are focused on similar target volumes but they differ in their dose, fractionation, adjuvant scheduling and surgical timing. There are basic science reasons for these different approaches so as to affect tumor cell repopulation which also influence the post-treatment toxicity encountered. We have included a trans-Atlantic approach in this section for a reason since conceptual differences in RT use exist between Europe and North America. For example, short-course RT is a northern European treatment and long-course neoadjuvant therapy is more North American. The strength of these approaches has been evaluated in well-constructed and well-powered trials where the two approaches (short-course *vs.* long-course RT) have been trialed in 2 distinct randomized studies.

Preoperative Radiotherapy: The Short Course

We have emphasized the Swedish approach in this section for a reason. Although other major trials followed suit the principal impetus for short-course RT was the original Swedish Rectal Cancer Trial (Stockholm I) which established the 5 × 5 Gy protocol [2, 3]. The trial randomized patients all with operable rectal cancer to either receive preoperative RT (as designated) or to proceed straight to surgery. The idea behind the fractionation was to replicate the larger RT doses used at the time. There are some very interesting findings when we revisit the results of this trial. Firstly, there was a marked reduction in the locoregional recurrence rates between the RT-treated and the non-RT-treated groups (11% vs. 27%, respectively; $P < 0.001$). This effect was spread with statistical significance across all stages and was associated with an improvement in cancer-specific overall survival with irradiation. The irradiated group, however, showed a considerably higher morbidity (including devastating anastomotic leakage) which extended to all stages. I remember attending many international surgical meetings where there was vociferous argument concerning the balance of severe complications in patients with Dukes' A (Stage I) disease where the survival benefit experience by irradiation was minimal and where there was a blanket policy (at least in Sweden) of preoperative RT use [4]. In this trial it was suggested that improvements in survival reflected the impact of preoperative RT on the local recurrence rate. This issue is complex and we should be reminded that we are interpreting results in an era when locoregional recurrence was common and when there was no standardized TME surgery.

The Stockholm I trial evaluated preoperative RT in operable rectal cancer on 849 patients between 1980 and 1986. The objective of Stockholm II was to reduce the attendant morbidity particularly in elderly patients with preoperative RT. The second study was initiated in March 1987 and included 557 patients through to May 1993 [5]. Similar results were noted with a reduction in locoregional recurrence rates with preoperative RT (12% vs. 25%, respectively; $P < 0.001$) and an improvement in overall survival (46% vs. 39%, respectively; $P < 0.03$). The survival benefit was somewhat offset in older patients by an increased intercurrent death rate in the irradiated cases which did not prove significant (19% vs. 12%, respectively; $P = 0.1$) Most of this effect was an increase in cardiac deaths in elderly patients who had undergone surgery with curative intent.

This data now (although it paved the way for preoperative RT), must be taken in my view with a grain of salt. The introduction of standard TME practice significantly reduced the locoregional recurrence rate (LRR) not only in Sweden but elsewhere throughout Europe somewhat *ex parte* of a blanket policy towards RT use [6]. Moreover, the Swedish data shows that a combination of preoperative RT with TME has reduced the LRR to about 1.5% within the first 2 years after surgery when non-randomly compared with historical controls undergoing TME alone. The latter is still considerably lower than traditional LRR rates after rectal resections with curative intent in Sweden, showing the impact of both advances in care. The beneficial effect improvement of preoperative RT is small suggesting that not all patients needed its addition. The issue of surgical technique and its impact in the context of RT use was addressed by the Dutch Rectal Cancer Trial which was partly instituted to assess in the burgeoning TME era, the strict necessity of short-course RT [7].

As stated this arose because the validity of the conclusions of Stockholm I and II were questioned given the moderately high reported LRR [8]. Even though there are biases in the Dutch TME trial, attempts were made to standardize the TME surgery (where every surgeon was evaluated and accredited) and where histopathological assessment (all pathology and CRM's) were separately evaluated. The Dutch trial randomly assigned 1861 patients showing an effect on LRR (2.4% vs. 8.2%, respectively; $P < 0.001$) confirming the benefit of preoperative short-course RT in the new TME era. In addition importantly, the advantage for LRR was maintained over a 12-year follow-up (5% vs. 11% respectively; $P < 0.0001$) [9] with an improvement in cancer-specific survival in those stage III cases where the CRM was negative. Not content with these results, the MRC CR-07 trial strengthened this data [10] where 1350 patients were randomly assigned to preoperative RT (25 Gy/5 F) or to initial surgery with a selective policy towards postoperative chemoradiation (45 Gy/25 F + 5FU) if the CRM was positive. There was a 61% reduction in the relative risk of LR by preoperative RT (4.4% vs. 10.6% respectively at 3 years). The data are limited by TME procedures being performed in only half the cases and by a high CRM involvement in abdominoperineal resection (APR) specimens. As pathologic assessments of these specimens have since been standardized (as has the technique of extralevator APR), in retrospect, the interpretative value of this study seems to be fairly limited. On the plus side, however, a complete TME and preoperative RT virtually eliminated LR (<1%).

Long-Course Chemoradiotherapy

The use of neoadjuvant therapy was an extension of postoperative CRT and the preoperative approach is designed to reduce radiation toxicity, enhance the chances of a sphincter-saving procedure and improve overall survival. The widespread use of this technique was in part based upon the German CAO/ARO/AIO 94 trial which randomized T3, T4 or node-positive cases to either preoperative CRT or to postoperative CRT [11]. In this trial, 421 patients were randomly assigned for preoperative CRT with 402 postoperative CRT cases resulting in a significant reduction in the LRR in the preoperatively treated cases (6% vs. 13%, respectively; P = 0.006). The overall survival between the groups was similar. The effect on the LRR was durable to 11 years of follow-up [12] without any impact on disease-free survival or overall survival. Toxicity was less in the preoperative group but there was no difference specifically in the anastomotic leakage rates.

Not to be outdone, the NSABP R-03 Trial also compared preoperative CRT with postoperative CRT in T3 or T4 node-positive cases, however, this study was truncated early because of poor recruitment significantly underpowering the study. Despite this, interim analysis of 267 patients (when they actually wished to accrue 900 patients), showed a better disease-free survival (DFS) in the preoperative group [13]. The LRR and the overall survival (OS) rates were however, no different.

Short-Course Versus Long-Course Trials

The goals of short-course and long-course therapy are a little different. Short-course treatment provides exceptional local control when combined with a quality TME as clearly shown in the Dutch Rectal Cancer Trial. Those exponents of long-course therapy would point to improvements in sphincter preservation and rather low radiation toxicity with small fractions. In advanced cases, the issue of additive CT has been addressed in two major trials which have shown a reduced risk of distant failure. One French trial was initiated in part for T3 and T4 tumors where preoperative RT was part of traditional treatment. The FFCD 9203 Trial compared preoperative standard RT (45 Gy/25 F over 5 weeks) with preoperative CRT (5FU and leucovorin W1/W5) [14]. The LRR was lower with preoperative CRT although OS was similar between the groups. The European Organization for the Research and Treatment of Cancer Group conducted the EORTC 2291 Trial randomizing 1011 T3/T4 cases to 4 separate arms; namely, preoperative RT, (45 Gy/1.8 Gy per F) preoperative CRT, (5FU + leucovorin) preoperative RT + postoperative CT and preoperative CRT + postoperative CT [15]. The study showed no differences in DFS or OS between groups however, when RT alone was used there was a higher LRR [16].

Analyzing the trials I have discussed above does not permit a short- vs. long-course comparison as the patients recruited were very different. In this regard, the Swedish I and II, the Dutch TME and the MRC CR-07 trials were designed for

resectable T1-T3 lesions whereas the German CAO Trial and the NSABP R03 trial were designed for T3/T4 cases. Here there are two relevant trials to consider. The first was the Polish Trial which was designed in part to determine if long-course CRT improved sphincter preservation, however, it was a randomized trial comparing short-course preoperative RT (25 Gy/5 Fr) with long-course CRT (50.4 Gy/1.8 Fr + bolus 5FU + leucovorin). In this trial adjuvant postoperative CT was not mandatory [17]. This trial assessing T3 or T4 low rectal cancers without sphincter infiltration showed no difference in sphincter preservation rates between groups (61% short-course vs. 58% long-course; P = 0.57), or in overall survival, (67.2% vs. 66.2%, respectively) relapse-free survival (58.4% vs. 55.6%, respectively) or LRR (9% vs. 14.2%, respectively).

The second similar trial was conducted in Australasia by the Trans-Tasman Radiation Oncology Group for T3 localized cases, the TROG-01-04 Trial [18]. In this trial all patients received adjuvant CT. The LRR was 7.5% vs. 4.4% respectively (NS) with no differences in distant recurrence, DFS or OS. Summarizing this data, both the Polish and the Trans-Tasman trials failed to significantly reduce the risk for an APR with long-course CRT. The likelihood here is that the scheduling did not induce sufficient downsizing of the tumor, with clinical decision-making towards APR based upon a preoperative tumor level rather than the tumor responsiveness. The outcomes following the trend towards waiting longer before surgery (particularly in low tumours) designed to determine pathological complete response (pCR) are awaited and will affect future decision making. These changes in rectal cancer management have re-emphasized distant failure in rectal cancer which still persists at 25% or so after preoperative RT and which is unaffected by a long-course régime.

The role and scheduling within standardized protocols of additional pre-surgical and postoperative CT remains to be determined and selected. In this respect, since 30% of patients with locally advanced disease actually die from their metastases, the use and type of adjuvant and interim neoadjuvant CT takes on a particular importance and will be affected by compliance in those cases deemed higher risk for microscopic disease outside the pelvis. The personalized approach is dependent upon the tumour population of practice. At one end of the spectrum there may be a selective reduction in the intensity of treatment with a wait and watch policy in low lying small tumours, whereas at the other end of the spectrum the density of therapy will need to be increased by adding neoadjuvant CT before CRT in the advanced case [19]. This approach has led to more novel preoperative strategies incorporating oxaliplatin [20] capecitabine + oxaliplatin and the addition of bevacizumab [21, 22].

As a further assessment, Stockholm III has randomized patients to three treatment régimes; namely, short-course RT with standard surgery at 1 week, or at 4–8 post-RT weeks *vs.* long-course RT and delayed surgery [23]. The aim here is to permit more downstaging and sphincter preservation and to obviate postoperative complications. The right combination here with an incorporation of postoperative adjuvant CT to reduce distant metastases, remains to be decided. A further strategy with the benefits of short-course therapy will be the incorporation of preoperative CT in the interval between RT and surgery and this has been addressed by the

RAPIDO (**R**adiotherapy **A**nd **P**reoperative **I**nduction followed by **D**edicated **O**peration) trial with short-course RT followed by standard dose CT (capecitabine + oxaliplatin prior to surgery) [24].

The benefit of RT for OS remains elusive where preoperative RT increases surgical morbidity and delays the administration of adjuvant CT [25, 26]. Given that RT may also be associated with sexual and anorectal dysfunction as well as an increased risk of a second malignancy, the onus is on selectivity of treatment [27–29]. This approach will also limit the use of RT as an adjuvant in those at risk of distant metastases particularly as full-dose systemic therapy in such cases may be delayed for as much as 4 months. The MRI can clearly act as a decision tool with more aggressive tumor risk factors; namely, mesorectal fascial (mrf) involvement, tumor extension into the mesorectal fat, tumor location, perineural invasion, extranodal deposits and MRI evidence of extramural vascular invasion (EMVI). Although this approach has been advocated by the MERCURY Study Group this data are not yet validated. In this data, however, MRI CRM positivity is the only preoperative staging parameter which correlates directly with OS, DFS and LRR. In this group's good prognosis patients treated by TME surgery alone, (i.e. a safe CRM and T2 or T3a/b cases) there was an acceptable LRR of 3% with a 5-year OS of 68% and a DFS of 83% [30, 31].

An overall survival benefit was seen with the Swedish Rectal Cancer Trial and also in a meta-analysis of preoperative RT trials when an adequate radiation dose was used (corresponding to a biologically effective dose >30 Gy) [32]. The controversial issues here include the optimal fractionation, the timing of surgery and the best CT combination and scheduling. Short-course RT is associated with short- and longer-term morbidity and this has even been unfavourably compared to long-course RT [33–35]. As discussed, Stockholm III was initiated by the Stockholm Colorectal Cancer Study Group (the SCCSG) randomizing patients with resectable rectal cancer to either short-course RT (5 × 5 Gy) with surgery within a week or surgery after 4–8 weeks or long-course preoperative RT (25 Gy) with surgery at 4–8 weeks. Delaying surgery is associated with a significant reduction in postoperative complications without any negative oncological impact. This has led to a series of criteria which are followed by radiologists after neoadjuvant CRT in an effort to decide about complete clinical responsiveness (cCR) and of the place for organ preservation. But there are some caveats to this oft quoted Stockholm III study where the running of this non-inferiority protocol was a little unusual. The initial study protocol (SCRT + immediate surgery, SCRT + delayed surgery and LCRT) was altered to a two-arm randomization because of insufficient RT services in the participating hospitals and this created a bias away from long-course RT recruitment. Moreover, the analysis was biased towards the 3-arm and the 2-arm assessments.

Concerns about the use of long-course RT in the delays in treatment and the risk of distant metastases is obviated with concomitant CT which also improves local control [15, 36]. This issue is not absolutely decided, however, since an excessive delay in surgery (out to 11 weeks or beyond) has been shown by the French GRECCAR group to be associated with a higher postoperative morbidity [37]. With this data, distant metastasis is now the major cause of rectal cancer relapse [38, 39]

where scheduling is critical and where it has been suggested that a delay in CT use compromises survival [40]. The current concerns that a delay in surgery will compromise outcome do not appear substantiated. Additionally, the benefit of adjuvant CT after preoperative CRT is unclear but there may be benefit of short-course RT with an operative delay where upfront CT could selectively be administered to high risk cases for distant metastases during this waiting period after RT completion. This is of course the basis of the RAPIDO trial and of a recent Polish series [41]. The goals in this treatment are, however, somewhat mixed. Some will want to further reduce LR along with toxicity and postoperative complications whereas other régimes are aimed at interim distant metastatic disease.

Professor Glimelius addresses many of the controversial issues with adjuvant RT in an important recent article [42]. The Swedish division into the 'good,' 'bad' and 'ugly' categories; namely low, intermediate and high risk variants respectively, has been made for management reasons even when there is no universal consensus on the definition of each group. Nevertheless, the division routinely substages cases using MR imaging and MDT counseling which will have secondary outcome benefits. Ostensibly the early (good) case is resected without pretreatment where the risk of locoregional recurrence is very low following a TME. The assessment here is the benefit ratio of CRT which has reduced the risk of LRR by a significant factor, but in this group the absolute gain is low enough that such treatment is not justified [43, 44] even when the radiation techniques have improved so that the attendant morbidity is small. The aim here is to define those cases suitable for local excision where the risk of failure is very low (cT1sm1-2). The subgroups which extend this view will include the cT1-2, some cT3ab and even some cT3c cases (provided that the latter are not too distally located and that these tumours are designated mrf-negative with a clear distance of >1 mm to the mesorectal fascia on MR imaging). Those intermediate (bad) cases do well with a TME but the risk of recurrence is that of the Unit surgeons performing the surgery. There are no data suggesting advantage of the long- over the short-course RT in these patients where one is trying on the loosest of grounds to reduce the risk of LRR. The use of long-course treatment here will only just increase morbidity for no added benefit. The subgroup of bad examples where there will be long-course benefit include low cases which are cT2-3a, cT3cd, cT4ab, however, one may decide in an anterior case not to use such adjuvant treatment, deciding rather to just resect the posterior wall of the vagina *en bloc*.

It is of course the ugly tumour (the cT3mrf + or the cT4b case) where CRT is typically used. The debate lies in how much to delay the surgery with an increasing trend towards delay so that an adequate down staging is achieved and so that the pCR rate is enhanced. The data here are currently conflicting where the French Phase III study already mentioned headed by Lefevre [37] randomized cT3/4 or TxN+ tumours of the mid- and lower rectum receiving 45–50 cGy with 5FU or Xeloda to surgery at 7 or 11 post-treatment weeks, (NCT01648894) showing no difference in the primary endpoint of pCR (ypT0N0) (15 vs. 17.4% respectively) but where in the delayed surgical group there was a substantially higher morbidity and an overall worse quality of the TME specimen. By contrast a British study reported by Evans et al. [45] and presented at the ESMO conference (but only so far

published in abstract form), showed the opposite effect using MRI down-staging in follow-up where a 12 week as opposed to a 6 week wait improved the pCR and the mrTRG. For ugly tumours, the response can be predictive since a lack of response to RT/CRT may indicate a lack of responsiveness to supplemental CT [46]. Again, higher RT doses will also in selected cases lead to higher pCR [47].

The British medical oncologist Rob Glynne-Jones has made the point that in our trials we may well be simply looking the wrong way [48]. Most of the trials are underpowered and have failed to stratify risk in rectal cancer cases, assessing only LRR or using currently unvalidated end-points such as the pCR. He is right when he suggests that at the current moment, the results of many studies will not be able to influence individual patient management. Our current endpoints of local recurrence and metastatic disease also reflect different propensities in different types of tumours. Locoregional recurrence is a measure of a more advanced tumour stage, surgical precision and local mesorectal fascial involvement. Even when some cases have a low risk of local recurrence, however, they still have a propensity to metastasize, an outcome which is less related to surgical prowess. The challenge now with rectal cancer is more the targeting of systemic disease devising measures which will increase the pCR (particularly after more adventurous chemotherapy and targeted biologic therapies). In these patients local control is not the issue and the addition of a radiosensitizing agent such as irinotecan or oxaliplatin will have little influence.

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Chapter 21
Radiation Therapy: The North American Approach

Ryan M. Lanning and Karyn A. Goodman

Introduction

The treatment of rectal cancer is evolving and the role of radiotherapy (RT) continues to be refined. Treatment options and regimens often depend upon the stage of disease, imaging findings, or surgical pathology. Radiation therapy is used in the treatment of locally advanced rectal cancer in the neoadjuvant setting or as post-operative therapy for tumors with high-risk histopathologic features. In the modern era of total mesorectal excision and induction or adjuvant chemotherapy, the primary benefit of radiation is local control. Rectal cancer is unique in that locally recurrent lesions can cause significant symptoms of pain, bowel obstruction and rectal bleeding. Additionally, locally recurrent disease often requires significant surgery such as a pelvic exenteration. Neoadjuvant RT can also reduce the extent and morbidity of surgery and increase the rates of sphincter preservation.

This chapter will review the implementation of RT in rectal cancer as practiced in North American cancer centers.

Locally Advanced Rectal Cancer: Neoadjuvant Chemoradiation

In locally advanced (T3–4, N+) rectal cancer, the locoregional recurrence (LRR) rates with surgery alone using blunt dissection range from 30% to 60% [1, 2]. The addition of post-operative 5-fluorouracil (5-FU)-based chemoradiation (CRT) has reduced recurrence rates down to 10–14% on average with an improved overall

R. M. Lanning · K. A. Goodman (✉)
Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: KARYN.GOODMAN@ucdenver.edu

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survival (OS) of between 10% and 15% [3–5]. In North America, these findings led to a National Institutes of Health consensus statement recommending adjuvant 5-FU-based CRT for Stage II–III rectal cancer [6].

A major advance in surgical technique in rectal cancer management was the introduction of the total mesorectal excision (TME) involving sharp dissection to the levator ani during low anterior and abdominoperineal resection. This has reduced the rates of positive or close circumferential margins and increased the number of lymph nodes resected, standardizing a quality assurance of rectal cancer excision worldwide. TME has vastly improved the oncologic outcomes; most notably the rates of local recurrence and the overall survival to rates similar to those achieved with post-operative chemoradiation [7]. Even with significantly improved surgical techniques, the Dutch TME trial (CKVO 95-04) demonstrated improved locoregional control with pre-operative radiation versus standardized TME alone [8]. This study randomized 1805 patients with any stage of primary rectal adenocarcinoma to short-course pre-operative RT (5 Gy × 5) followed by TME versus surgery alone. A significant improvement in local recurrence rate was seen at 2-years (2.4% vs 8.2%, $p < 0.001$) and was maintained out to 10-years of follow-up (5% vs 11%, $p < 0.0001$). Contrary to the earlier Swedish pre-operative short-course RT trial, no improvement in OS was observed, although the prior study did not require standardized TME surgery [9]. On an unplanned subgroup analysis, Stage III patients with negative margins after pre-operative radiation and TME demonstrated significantly improved OS (50% vs 40%, $p = 0.032$) [10]. Thus, even after improving surgery with TME, RT still provided a significant benefit in local control.

The sequencing of RT and surgery has also been evaluated in prospective studies. Pre-operative radiotherapy has hypothetical advantages including improved oxygenation to the tumor via undisturbed blood vessels, down-staging at the time of surgery, increased probability of negative surgical margins, more limited surgery (sphincter-sparing), and smaller radiotherapy fields which could improve treatment tolerance. Similarly, the delivery of chemotherapy to the tumor could also be enhanced in the neoadjuvant setting due intact vasculature. Additionally, earlier administration of chemotherapy may treat potential occult micrometastases. An early meta-analysis of 14 randomized control trials (RCT) comparing pre-operative RT with surgery alone demonstrated a significant reduction in odds of death and local recurrence by 16% and 51%, respectively [11].

The landmark German Rectal Cancer Trial (CAO/ARO/AIO-94) established neoadjuvant CRT as the current standard of care for locally advanced rectal cancer practiced in North America. This Phase III study randomized 823 patients with resectable cT3/4 or cN+ rectal adenocarcinoma to pre-operative infusional 5-FU-based CRT (50.4 Gy in 28 fractions) followed by TME and adjuvant 5-FU versus post-operative CRT with a similar schedule including a boost of 5.4 Gy to the tumor bed [12]. The primary outcome of a hypothesized difference in OS was not found. However, pre-operative 5-FU based CRT significantly reduced LR rates which persisted at 10-years (7.1% vs 10.1%, $p = 0.048$) and resulted in a pathologic complete response (pCR) rate of 8%, also increasing the rate of sphincter sparing surgery (39% vs 19%) in patients deemed to need an APR pre-CRT [13]. An

analogous trial in the United States (NSABP R-03) was closed early due to poor accrual. Interim results from 267 patients demonstrated improved disease-free survival (DFS) with pre-operative CRT, but no difference in 5-year LR (10.7%) [14]. The pCR rate with neoadjuvant CRT was 15%. Similar results were found for pre-operative short-course (5 Gy × 5) RT alone versus selective long-course post-operative CRT in the combined MRC CR07 and NCIC-CTG C016 trial for resectable rectal adenocarcinoma [15].

The benefit of concurrent CRT over RT alone on local control was confirmed in 2 large randomized control trials. The European Organization for Research and Treatment of Cancer (EORTC) 22,921 trial enrolled 1011 patients with resectable T3/T4 rectal adenocarcinoma and randomized them to a 2 × 2 design of pre-operative RT alone ± adjuvant chemotherapy versus pre-operative 5-FU based CRT ± adjuvant chemotherapy [16]. Adjuvant chemotherapy was 5-FU and leucovorin. The primary endpoint of a difference in OS or DFS with either pre-operative CRT or adjuvant chemotherapy was not met. An unplanned subgroup analysis suggested there may be a benefit of adjuvant chemotherapy on OS and DFS in good responders (ypT0-2) to neoadjuvant therapy [17]. Preoperative CRT promoted tumor down-staging more than RT alone (13.7% vs 5.3%, $p < 0.001$) [18]. Notably, a significant reduction in LR was found for pre-operative CRT over RT alone regardless of adjuvant chemotherapy (10-year LR = 11.8%/11.7% vs 22.4%/14.5%) [19]. The French FFCD 9203 trial included the same patient population (n = 505) investigating pre-operative RT versus CRT with all patients receiving adjuvant 5-FU chemotherapy [20]. The pCR was again significantly higher in the CRT group (11.4% vs 3.6%), however, the 5-year OS, PFS and rate of sphincter preservation were not different between treatment groups. Although not the primary endpoint, the 5-year LRR was significantly lower in the pre-operative CRT arm (8.1% vs 16.5%, $p = 0.004$).

Based on multiple RCT, neoadjuvant therapy is now the standard of care for locally advanced rectal cancer. The outcomes of the major trials are summarized in Table 21.1. A meta-analysis of 22 RCT concluded that neoadjuvant RT improved local control when compared with surgery alone and nearly exhibited a benefit in OS [21]. It also confirmed that neoadjuvant CRT further reduced local recurrence over RT alone, but not OS.

Replacing infusional 5-FU with the oral fluoropyrimidine capecitabine during concurrent CRT has been investigated to determine if there is a reduction in the burden of the continuous infusion pump on patients. The German Rektum-III study was a non-inferiority trial of capecitabine versus infusional 5-FU in the perioperative treatment of locally advanced rectal cancer. This study was initially designed to compare the 2 agents in post-operative CRT after TME with an R0 resection and pT3-4 or pN+ disease [22]. After the results of the German Rectal Cancer Trial showing a significant benefit in local control for neoadjuvant CRT, the study was modified to include this treatment. The results of the trial were within the pre-specified non-inferiority margin of a 12.5% difference in 5-year OS (76% capecitabine vs 67% 5-FU). At a median follow-up of 52 months, each treatment group had similar rates of LR (6% vs 7%), but those patients who received

Table 21.1 Neoadjuvant (chemo)radiotherapy for locally advanced rectal cancer

Study	Patients	Pre-operative RT	pCR (%)	10-year LR (%)	10-year OS (%)
Swedish Rectal Cancer Trial [9]	1147 resectable tumors	SRT	NR	9 (13-year)	38 (13-year)
Dutch TME Trial [10]	1414 cT1-4/N_{any}	SRT	1	5	49
German Rectal Cancer Trial [13]	799 cT3-4 or N+	CRT	8	7.1	59.6
NSABP R-03 [14]	267 resectable tumors	CRT	15	10.7 (5-year)	74.5 (5-year)
EORTC 22921 [19]	1011 cT3-4/N_{any}	LRT	4.6	22.4	49.4
		CRT	12.5	11.7	50.7
FFCD 9203 [20]	742 cT3-4/N_{any}	CRT	11.4	8.1 (5-year)	67.4 (5-year)
MRC CR07/ NCIC-CTG C016 [15]	1350 resectable tumors	SRT	0	4.7 (5-year)	70.3 (5-year)

pCR pathologic complete response; *LR* local recurrence; *OS* Overall Survival; *SRT* short-course radiotherapy (5 Gy × 5); *CRT* chemoradiotherapy; *LRT* long-course RT (45 Gy/25 fractions); *NR* not reported

capecitabine had significantly fewer distant metastases (19% vs 28%, p = 0.04). For neoadjuvant CRT, the capecitabine cohort had a higher pCR rate than 5-FU, although it was non-significant (14% vs 5%). Further supporting the use of either agent during CRT, the NSABP R-04 trial, which investigated the addition of oxaliplatin to standard fluoropyridimine-based CRT, included comparison arms of infusional 5-FU and capecitabine with early results showing no difference in rates of pCR, surgical down-staging, or sphincter sparing surgery [23].

The wide array of new cytotoxic and targeted agents has propagated numerous small phase II studies evaluating pCR rates. Based on promising results of these phase II studies [24, 25], there have now been four recently reported phase III randomized trials which have added oxaliplatin to 5-FU based pre-operative chemoradiation with the intent of improving pCR and disease-free survival. Both the ACCORD trial [26] and the STAR trial [27] found no difference in the pCR rate with the addition of oxaliplatin to standard 5-FU infusional chemotherapy and 50.4 Gy RT, however, the toxicity was significantly greater in the oxaliplatin arm. The NSABP R-04 [23] and the German CAO/ARO 04 study [28] which added oxaliplatin to continuous infusion 5-FU or capecitabine and 50.4 Gy of RT demonstrated that oxaliplatin did not result in an overwhelming improvement in the pCR rates, although it was statistically significant in the German study. The NSABP study showed significantly more Grade 3–4 diarrhea with oxaliplatin, similar to the STAR and ACCORD trials. Of interest, the toxicity in the oxaliplatin arm was not higher in the German study, likely due to a lower cumulative dose of oxaliplatin and a split course treatment with 5-FU. Oxaliplatin did not improve sphincter preservation in any of the studies; one of the goals of pre-operative therapy. In an update of the ACCORD trial, the 3-year actuarial rates of LC, DFS, or OS were found not to be statistically different [29]. In summary, oxaliplatin appears to only increase toxicity without improving pCR rates, sphincter preservation, or local control.

Bevacizumab, the partially humanized monoclonal antibody against soluble vascular endothelial growth factor (VEGF) is used in first-line therapy with standard chemotherapy for metastatic or recurrent colorectal cancer. The first clinical evidence of anti-angiogenic behavior when coupled with 5-FU chemotherapy was demonstrated for non-metastatic rectal cancer nearly a decade ago [30]. Since that time, there have been a number of trials incorporating bevacizumab with neoadjuvant chemoradiation. A Phase I/II study of 32 T3/T4 rectal cancer patients from the Massachusetts General Hospital demonstrated a 5-year LC and OS of 100% when bevacizumab was incorporated with 5-FU CRT (50.4 Gy) [31]. The pCR rate at the time of surgery was 16%. MDACC performed a similar phase I/II study adding bevacizumab to capecitabine-based chemoradiation in T3N1 and T3N0 rectal cancer patients. A 2-year LRR rate of 6.5% and a pCR rate of 32% in the 25 patients studied were reported. There were, however, a number of adverse events related to poor surgical healing including wound and anastomotic dehiscence requiring surgical intervention [32]. The ECOG 3204 multicenter trial added oxaliplatin and bevacizumab to standard capecitabine-based chemoradiation for 54 T3/T4 rectal cancer patients finding a pCR rate of 17% which was less than the cutoff of 30% needed to proceed with further study [33]. They also found increased delays in wound healing and 2 deaths during CRT, one attributed to therapy.

Another potential biologic target in rectal cancer is the epidermal growth factor receptor (EGFR). Two agents are available and used as FDA-approved first-line therapy for metastatic colorectal cancer, the partially humanized monoclonal antibody cetuximab and the fully humanized monoclonal antibody panitumumab. The EXPERT-C randomized trial sought to examine the addition of cetuximab to induction capecitabine and oxaliplatin chemotherapy as well as concurrent capecitabine-based CRT in resectable high-risk rectal cancer [34]. Of 165 randomly assigned patients, 60% were *KRAS* or *BRAF* wild-type, a predictive biomarker for good response to EGFR inhibition. The primary endpoint of improved complete response (pCR and radiological complete response) was not met (11% for cetuximab vs 9%). Both diarrhea and rash were increased during chemotherapy with the addition of cetuximab. At a median follow-up of 65 months, no benefit to cetuximab was seen in the entire population or *KRAS* wild-type patients with respect to PFS or OS [35]. A later unplanned subgroup analysis showed improved 5-year PFS and OS in patients who had *TP53* mutations regardless of *KRAS* mutant status. Another small phase II randomized trial (SAKK 41/07) studied the addition of panitumumab to capecitabine-based CRT (45 Gy) in 68 T3/T4 or node-positive *KRAS* wild-type rectal adenocarcinoma [36]. The primary combined endpoint of pCR and near-complete response was 53% with the addition of panitumumab versus 32%. Increased adverse events including diarrhea and anastomotic leakage were observed in the experimental arm.

At this time, there appear to be no additional agents to improve outcomes over standard 5-FU or capecitabine-based chemoradiation. The trials investigating these agents are summarized in Table 21.2. In summary, while the long-term results are pending from the 4 Phase III trials investigating oxaliplatin, it appears that the addition of oxaliplatin does not improve locoregional control or pCR and may only

Table 21.2 Prospective clinical trials of additional agents for neoadjuvant chemoradiation

Agent	Trial	N	CRT Treatments	pCR (%)	LRR (%)	DFS (%)	OS (%)	CRT Toxicity (Gr ≥ 3)
Oxaliplatin	ACCORD-12 [26, 29]	598	CAP + RT CAPOX + RT	13.9 19.2	6.1 (3-year) 4.4 (3-year)	68 (3-year) 73 (3-year)	88 (3-year) 88 (3-year)	10.9% 25.4%
	STAR-01 [27]	747	FU + RT FU + OX + RT	16 16	P	P	P	8% 24%
	German CAO/ARO/AIO-04 [28]	1236	FU + RT FU + OX + RT	13 17 (SS)	4.6 (3-year) 2.9 (3-year)	71 (3-year) 76 (3-year) SS	88 (3-year) 89 (3-year)	20% 24%
	NSABP R-04 [23]	1608	FU/CAP + RT FU/CAP + OX + RT	17.8 19.5	P	P	P	6.9% 16.5%[a]
Bevacizumab	MGH [30]	32	BV + FU + RT	16	0 (5-year)	75 (5-year)	100 (5-year)	D + HTN
	MDACC [32]	25	BV + CAP + RT	32	6.2 (2-year)	77 (2-year)	100 (2-year)	4%
	ECOG 3204 [33]	57	BV + CAPOX + RT	17	3.5 (cr)	P	P	53%
Anti-EGFR	EXPERT-C [34, 35]	165	CAP + RT CTX + CAP + RT	15 14	NR	68 (5-year) 75 (5-year)	72 (5-year) 84 (5-year)	2% 23%
	SAKK 41/07 [36]	68	CAP + RT P + CAP + RT	18 10	NR	NR	NR	D + Rash

N # Patients; *CRT* chemoradiotherapy; *pCR* pathologic complete response; *LRR* locoregional recurrence; *DFS* disease-free survival; *OS* overall survival; *Gr* grade; *CAP* Capecitabine; *RT* radiation therapy; *CAPOX* capecitabine and oxaliplatin; *FU* 5-flurouracil; *OX* oxaliplatin; *BV* bevacizumab; *D* diarrhea; *HTN* hypertension; *CTX* cetuximab; *P* panitumumab; *cr* crude rate; *NR* not reported; *P* pending; *SS* statistically significant

[a]gastrointestinal toxicity only

increase acute toxicity, particularly in the gastrointestinal tract. The three FDA-approved biologically-targeted agents for metastatic rectal cancer (bevacizumab, cetuximab, and panitumumab) also do not appear to improve outcomes in the general population of rectal cancer patients. Bevacizumab increases cardiovascular toxicities like hypertension and hinders wound healing. The EGFR-targeted agents may have an added benefit in specific subpopulations of rectal cancer patients based on mutational status, but these biomarkers require further testing.

Short-Course Versus Long-Course Radiotherapy

While the standard radiation approach in North America is CRT administered over 25–28 fractions, there is a competing approach in Northern Europe and Scandinavia involving short-course pre-operative RT alone based on the Swedish and Dutch trials. Short-course pre-operative RT involves administering a total dose of 25 Gy over 5 fractions. Much controversy and discussion exists regarding the advantages of either approach which are beyond the scope of this chapter. One potential difficulty making cross-trial comparisons is the inclusion of earlier stage disease in the short-course preoperative RT trials versus only Stage II or III disease in the CRT trials. Additionally, surgery is performed 4–8 weeks after CRT compared with 1 week or less following standard short-course radiotherapy which limits any potential surgical down-staging. There have been two major randomized trials, although limited in patient numbers and follow-up, which have addressed short-course RT versus long-course CRT.

The Polish Colorectal Study Group RCT included 312 patients with resectable cT3/4 rectal cancer and compared pre-operative RT (5 Gy × 5) followed by TME in 1 week versus pre-operative 5-FU based CRT followed by TME in 4–6 weeks. The sphincter-preservation rate was the primary endpoint [37]. Of note, TME was performed only for distal tumors, adjuvant chemotherapy was optional and there was no central review of the radiotherapy, surgical techniques, or pathology. Although short-course RT resulted in significantly more positive surgical margins (12.9% vs 4.4%, $p = 0.017$), there was no difference in 4-year OS (67.2% vs 66.2%), DFS (58.4% vs 55.6%), or LR (10.6% vs 15.6%). There was no significant difference in severe late toxicity (10.1% vs 7.1%) or permanent stoma rates (56.9% vs 51.6%), although these were numerically higher in the short-course RT group.

The more recent Trans-Tasman Radiation Oncology Group (TROG) Trial 01.04 enrolled 323 patients with cT3N0-2 rectal adenocarcinoma and randomly assigned them to short-course (5 Gy × 5) followed by surgery within 1 week or long-course 5-FU based CRT followed by surgery in 4–6 weeks [38]. Both treatment cohorts received post-operative 5-FU chemotherapy. The primary endpoint of the trial was the 3-year LR rate. At a median follow-up of 5.9 years, the 5-year LR rates were 7.5% and 5.7% for the short- and long-course treatment groups, respectively. These findings were not significantly different nor were the OS, PFS, or distant metastasis rates. On an unplanned subgroup analysis of distal tumors (<5 cm from the anal

verge), there was a difference of 12.5% in the cumulative incidence of LR favoring long-course CRT (12.5% vs 0%).

The duration of the interval between the completion of RT and surgery is undergoing investigation in several studies. Increasing the duration will likely allow additional treatment response observable on pathologic review. The Stockholm III trial included 303 resectable rectal cancer patients randomized to 3 pre-operative treatment arms: short-course RT followed by surgery within 1 week, short-course RT followed by surgery in 4–8 weeks and long-course RT (no chemotherapy) [39]. Interim analysis revealed a pCR of 12.5% in the short-course delayed surgery cohort versus 5% in the long-course RT alone cohort. More post-operative complications were found in the short-course RT followed by immediate surgery group (46.6% vs 40.0% vs 32%).

Short-course RT is also being combined with pre-operative chemotherapy in some trials. The currently accruing Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial randomizes non-metastatic locally advanced rectal cancer to pre-operative short-course RT followed by 6 cycles of capecitabine and oxaliplatin then surgery versus long-course CRT followed by surgery. The primary endpoint of this trial is the 3-year DFS [40].

Role of Radiation in Early Stage Rectal Cancer

Treatment of early stage (T1/T2 node-negative) rectal cancer balances survival and local control with functional outcomes. The primary treatment recommended is surgery with adjuvant therapy dictated by pathologic findings. Surgical options for early stage disease include local excision either by transanal excision (TAE) or transanal endoscopic microsurgery (TEMS) or conventional total mesorectal excision [41]. Selection of local therapy depends upon multiple factors including risk of nodal disease, pathologic characteristics and anatomical location and this issue is covered elsewhere in this book (Chap. 5, Part III).

From surgical series, the risk of lymph node metastases is approximately 10% and 20% for T1 and T2 tumors, respectively [41–44]. The risk of lymph node involvement is also increased in early stage tumors with lymphovascular invasion (LVI), deep infiltration into the submucosa and lower third rectal involvement. For low-lying tumors, invasion of the dentate line also significantly increases the risk for inguinal lymph node involvement with an odds ratio of nearly 24 [45]. A higher risk of lymph node involvement is an indication for an oncologic surgery (TME) and likely multimodality therapy. Oncologic outcomes for early stage rectal cancer depend upon the pathology of the surgical specimen. Willett et al. showed that T1/T2 tumors treated with local excision exhibited significantly reduced 5-year recurrence-free survival (RFS) and local control (LC) in poorly differentiated tumors or those with lymphovascular invasion (RFS = 87% vs 57% / LC = 96% vs 68% in combination), while LVI was only associated with worse RFS and LC in abdominoperineal resections (RFS = 91% vs 73% / LC = 92% vs 80%) [46]. Distal

rectal cancers represent a group where the morbidity of surgery may be minimized by other approaches.

Given evidence for a population of early stage disease found to have good local control after local excision and efforts to reduce the morbidity associated with radical resection, trials evaluating trans-anal excision have been performed. RTOG 89-02 was a Phase II multi-institutional trial of sphincter-sparing surgery for distal (≤10 cm from anal verge) and mobile rectal cancer ≤4 cm in diameter occupying less than or equal to 40% of the rectal circumference [47]. Based on the surgical pathology after gross total resection, patients were allocated to 3 different treatment groups: observation (T1, negative margins, ≤3 cm, no LVI, and normal serum CEA), 5-FU based post-operative CRT to 45–50.4 Gy with a boost to 50–56 Gy (>T1, and negative margins), or 5-FU based post-operative CRT to 45–50.4 Gy with a boost to 59.4–65 Gy (close or positive margins). At a median follow-up of 6.1 years, the 5-year LRR was 12% (14% for higher risk CRT groups) with no difference in OS or DFS between regimens. A similar Phase II prospective study by the CALGB (8984) examined T1/T2 tumors with the same anatomical inclusion criteria treated with local excision and post-operative 5-FU based CRT to 54 Gy (T2 lesions) [48]. After a median follow-up of 7.1 years, the 10-year LRR was 8 and 18% for T1 and T2 lesions, respectively. Recurrences occurred earlier in patients with T2 disease (2 vs 4 years) [49]. The 10-year OS was low for T2 lesions treated with local excision and post-operative CRT (66%) when compared with T1 lesions after local excision alone (84%). Notably, neither of these previous studies was conducted during the era of pre-operative endorectal ultrasound or MRI which is now routinely used to assess the extent of disease and lymph node involvement.

Improved local control with neoadjuvant chemoradiation in the locally advanced setting has led to studies examining its role in T2 disease treated with local excision. This is particularly relevant in distal tumors where sphincter-sparing surgery may not be possible making a permanent colostomy unavoidable. The American College of Surgeons Oncology Group (ACOSOG) recently reported the early outcomes of a Phase II study investigating neoadjuvant capecitabine- and oxaliplatin-based CRT followed by local excision in T2N0 distal (≤8 cm from the anal verge) rectal cancer (ACOSOG Z6041) [50]. Both the capecitabine and radiation dosage were reduced on interim analysis due to increased grade 3 adverse events. The pCR rate for 77 evaluable patients was excellent at 44% with only 1 positive surgical margin. The primary endpoint of disease-free survival at 3 years was 88% [51].

The NCCN defines strict criteria for local excision of T1N0 tumors which include mobile well – moderately differentiated lesions <3 cm in size, <30% circumferential involvement, wide margins (>3 mm), tumors located within 8 cm of the anal verge and no LVI or perineural invasion. T2N0 tumors are currently recommended to undergo transabdominal resections. Although there is prospective evidence to support minimizing surgical interventions and potential morbidity with combined modality therapy (Table 21.3), caution is advised in the absence of adjuvant therapy even for small node-negative lesions. A large retrospective cohort study by Memorial Sloan Kettering Cancer Center (MSKCC) comparing radical resection and transanal excision for nearly 300 patients with T1N0 disease demonstrated significantly

Table 21.3 Prospective clinical trials with radiotherapy in early stage rectal cancer

Study	N	Tumors	Surgery	Treatments	10-year LR (%)	10-year OS (%)
RTOG 89-02 [47]	72	Mobile, ≤4 cm, ≤ 40% ccm, distal	LE	1. Observation 2. Post-op CRT (50–56 Gy) 3. Post-op CRT (59.4–65 Gy)	12 (5-year)	NR
CALGB 8984 [49]	110	T1/T2, ≤4 cm, ≤ 40% ccm, distal	LE	T1: Observation T2: PORT (54 Gy) + 5-FU	8 18	84 66
Lezoche et al. [161]	100	cT2N0M0, G1-2 <3 cm, DAV ≤6 cm	ELRR vs TME	Neoadjuvant CRT (50.4 Gy)	12 10	72 80
ACOSOG Z6041 [51]	90	cT2N0, ≤4 cm, ≤ 40% ccm, DAV ≤8 cm, mobile	LE	Neoadjuvant CAPOX CRT (50.4–54 Gy)	44% pCR	3-year DFS 88

N # patients; *LR* local recurrence; *OS* Overall Survival; *ccm* rectal circumference; *LE* local excision; *CRT* chemoradiotherapy; *DAV* distance from anal verge; *ELRR* endoluminal locoregional resection; *TME* total mesorectal excision; *CAPOX* capecitabine and oxaliplatin; *pCR* pathologic complete response; *NR* not reported

worse local recurrence in those undergoing transanal excision (13.2% vs. 2.7%) and disease-specific survival (87% vs. 96%) at 5-years [52]. This data should be viewed with caution as the transanal excision group were notably older (mean age 64 years vs. 59 years) with a shorter mean distance of the tumor from the anal verge (5.9 cm vs. 7.8 cm) and a smaller tumor size (2.3 cm vs. 3.1 cm).

Post-Operative Radiation Therapy

Historically in North America, locally advanced rectal cancer was treated with radiation in the post-operative setting. The 2001 meta-analysis by the Colorectal Cancer Collaborative Group that included 7 randomized control trials of post-operative RT demonstrated no benefit in mortality, but a significantly decreased risk of local recurrence by 37% (5-year LR = 15.3% vs 22.9% curative surgery alone) [53]. The landmark German Rectal Cancer Study Group trial established the benefit of pre-operative over post-operative CRT for local control and toxicity. Since that time, the vast majority of locally advanced rectal cancer patients receive neoadjuvant therapy. However, some patients are under-staged pre-operatively and found to have T3/T4 or node-positive disease at the time of surgery for which adjuvant CRT is standard of care. Additionally, histopathologic adverse risk factors in early stage (T1/T2) disease including poor differentiation (tumor grade 3 or neuroendocrine features), positive surgical margins and lymphovascular invasion indicate a higher risk of recurrence and potential benefit of adjuvant chemoradiation. In these settings,

post-operative RT still plays a role and the Radiation Oncologist should understand the reasoning for and implications of treatment.

There are 5 major trials that defined the role of post-operative CRT for locally advanced rectal cancer (Table 21.4). The impact of these trials on current rectal cancer management arises from the pooled analysis by Gunderson et al [54] Using the results of prior studies, they defined different risk groups for recurrence based on T and N stage. The stratified groups include intermediate (T1-2/N1 and T3N0), moderately high (T1-2/N2, T4N0, and T3N1) and high (T3N2 and T4/N1-2) risk groups [54]. Each risk group has a different OS, DFS, local recurrence and DM rate with respect to therapy received. Although not compared statistically and limited in some cases by the number of patients at risk, the intermediate risk group emerges as one that may only require close observation, adjuvant radiation, or chemotherapy alone given limited numerical improvement in outcomes with CRT.

Evaluation of the need for post-operative radiotherapy should also include factors related to the surgical management as well as histopathology. The modern oncologic surgery is TME which improves local control, overall survival and cancer-specific survival when compared with conventional blunt surgical resection [7]. While the large post-operative randomized controlled trials did not standardize surgical technique according to TME criteria, important findings regarding surgical parameters have been reported. A secondary analysis of the Intergroup 0114 post-

Table 21.4 Randomized trials investigating post-operative radiotherapy in rectal cancer

Study	N	Tumors	Treatments	5-year LR (%)	5-year OS (%)
NCCTG 79-47-51 [4]	204	pT3-4 or N1-2	1. PORT (45–50.4 Gy) 2. PORT + SEM + bolus 5-FU → AC	25 (7-year) 14 (7-year)	48 56
NCCTG 86-47-51 [5]	660	pT3-4 or N1-2	1. 5-FU ± SEM → PORT + bolus 5-FU → AC 2. 5-FU ± SEM → PORT + PVI 5-FU → AC	53 (4-year) 63 (4-year)	60 (4-year) 70 (4-year)
Intergroup 0114 [162]	1695	pT3-4 or N1-2	5-FU ± LC ± LV → PORT + bolus 5-FU ± LC → AC*	9 ⊥ 18+	76⊥ 55+
NSABP R-01 [163]	555	pT3-4 or N1-2	1. Observation 2. Adjuvant MOF 3. PORT (46–53 Gy)	25 (5-year abs) 21 (5-year abs) 16 (5-year abs)	43 53 41
NSABP R-02 [164]	694	pT3-4 or N1-2	1. Adjuvant MOF or bolus 5-FU + LV 2. PORT (50.4 Gy) + 5-FU → AC	13 8	~65 ~65

N # patients; *LR* local recurrence; *OS* Overall Survival; *NCCTG* North Central Cancer Treatment Group; *NSABP* National Surgical Adjuvant Breast and Bowel Project; *PORT* Post-operative radiation therapy; *SEM* semustine; *AC* Adjuvant chemotherapy; *5-FU* 5-fluorouracil; *PVI* prolonged venous infusion; *LC* leucovorin; *LV* levamisole; MOF: 5-FU, semustine, and vincristine

⊥: T1/2, N+ /T3N0; +: T3N+/T4

*: Various adjuvant chemotherapy regimens

operative CRT study revealed that for node-negative patients (N = 527), examination of ≥14 lymph nodes in the surgical specimen significantly reduced the 5-year recurrence rate (19% vs >30%) and increased OS (~10% increase) [55]. The improved oncologic outcomes with increased lymph nodes evaluated in node-negative disease are most likely due to missed positive lymph nodes. Although the data are limited, in the era of TME and neoadjuvant CRT, the number of lymph nodes retrieved is likely less important given both the more extensive lymphadenectomy associated with TME and the pre-operative treatment response [56].

If post-operative radiotherapy is determined to be necessary based on understaging, histopathologic features, or limited surgery, the remaining parameter is the scheduling of adjuvant chemotherapy and radiation. A Korean trial randomized 308 patients with Stage II/III rectal adenocarcinoma to early or late 5-FU-based CRT sandwiched into adjuvant chemotherapy [57]. The study did not find a significant difference in the primary endpoint of disease-free (10-year = 71% vs 63%) or overall survival between the 2 groups. On an unplanned post-hoc analysis, patients who underwent an abdominoperineal resection experienced significantly higher DFS with early CRT (63% vs 40%) likely related to the high risk of local recurrence in patients with distal rectal tumors. However, this study did not evaluate the use of FOLFOX chemotherapy, the regimen now used as adjuvant therapy and therefore, the benefit of the earlier RT may not be as evident with more effective systemic therapy.

Tailoring Neoadjuvant Therapy: Non-Operative Management, Omission of Radiotherapy, and Total Neoadjuvant Therapy

Although, the combination of (chemo) radiotherapy and surgery improves oncologic outcomes, it can come at the cost of significant toxicity. In the large RCTs of neoadjuvant RT and CRT, rates of perioperative mortality ranged from 0.7% to 3.5% and about one-third of patients experienced post-operative complications [13, 14, 16, 20, 58]. In high-volume experienced cancer centers, the perioperative mortality and morbidity is lower (0.4% and 25%, respectively), but still present [59]. While there are differences in acute side effects dependent on the use of concurrent chemoradiotherapy or RT alone, the long-term side effects of both approaches are undeniable. Both sexual and bowel function are found to be significantly altered in >50% patients after combined modality therapy [60, 61]. In light of the potential morbidity and mortality associated with combined modality therapy, investigators have examined omitting portions of standard therapy in select individuals.

Pre-operative therapy provides a unique opportunity to assess treatment response and individualize patient care. Pathologic complete response at the time of surgery has been shown to correlate with improved long-term oncologic outcomes including LR [62], DFS [63] and OS [64]. Admittedly this has yet to be directly tested in a large RCT, however, it does indicate that there may be a population of patients who derive little benefit from additional therapy. The inclusion of adjuvant chemother-

apy is also being questioned as potentially lacking any additional benefit over pre-operative therapy. A recent meta-analysis investigating the individual results from nearly 1200 patients in 4 phase III trials indicated there was no improvement in OS, DFS, or distant recurrences with the addition of post-operative fluorouracil-based chemotherapy [65]. However, there was a possible DFS benefit in patients with proximal tumors.

Non-operative management or the "wait-and-see" approach has been investigated in small retrospective and prospective studies. This issue is covered in more detail elsewhere in this book (Chap. 12, Part IV). Following neoadjuvant CRT, the patient is evaluated by clinical and radiographic examination for evidence of disease. This typically occurs 6–8 weeks post-therapy in order to allow time for disease response and regression. Individuals with a clinical complete response (cCR) are considered for routine surveillance instead of the standard TME.

In this regard, long-term outcomes of non-operative management were first reported by Habr-Gama et al. [66]. This retrospective study included 265 Stage II–III distal (0–7 cm from the anal verge) rectal adenocarcinoma patients treated with standard 5-FU-based CRT without any adjuvant chemotherapy. Eight weeks after CRT, 71 patients (26.8%) were found to have a cCR and did not undergo TME. After a mean follow-up of 57.3 months, only 2 patients (2.8%) in the observation group developed local recurrence, while 4.2% developed distant metastases. The 5-year DFS and OS rates were 92% and 100%, respectively. These outcomes were similar to a group of 22 patients undergoing TME found to have a pCR at the time of surgery. An updated report in 2006 included a total of 99 Stage I–III distal rectal adenocarcinoma patients managed non-operatively after 12-months of close observation without evidence of disease [67]. At a mean follow-up of 60 months, this group experienced a total of 13 recurrences, 5 of which were isolated endorectal recurrences (5%). Confirming their original report, the 5-year DFS and OS remained high at 85% and 93%, respectively. Although the numbers are small, the group with recurrent disease (distant and local) experienced significantly worse overall survival.

Based on the encouraging results from retrospective pilot studies, a prospective cohort study was performed in the Netherlands by Maas et al. [68] in locally advanced or distal tumors with 1–3 involved lymph nodes. After CRT with capecitabine, patients with a cCR were offered enrollment on the trial in the "wait-and-see" cohort. A cCR was strictly defined based on MRI criteria, absence of tumor on endoscopy, negative biopsy and no palpable tumor on digital rectal examination (DRE). Twenty-one patients were included in the observation cohort and underwent a rigorous follow-up protocol including DREs, MRI, endoscopy with biopsies, CT scans of the chest and abdomen and serum CEA measurements every 3–6 months. Any patients with clinically positive LNs prior to neoadjuvant therapy received adjuvant CAPOX chemotherapy for 6 cycles. After a mean follow-up of 25 months, 1 of the 21 patients managed non-operatively developed a local recurrence which was successfully salvaged surgically. The 2-year DFS and OS were 89% and 100%, respectively, which was not different from a pCR control group of 20 patients [68]. Regarding treatment toxicity, multiple bowel function parameters

as assessed by the MSKCC bowel function score were significantly better in the "wait-and-see" group than those who underwent a TME. This study further confirmed good oncologic outcomes with non-operative management as well as less treatment morbidity with respect to bowel function.

Subsequent single institutional reports have confirmed excellent outcomes with non-operative management. Investigators from MSKCC reported retrospectively collected outcomes for 32 patients treated with neoadjuvant CRT who developed a cCR and elected to forgo surgery [69]. cCR was defined by clinical examination and endoscopy alone. Close follow-up every 3–6 months was performed at the discretion of the treating physician. The majority of patients undergoing non-operative management were older with lower stage disease or distal rectal tumors. Six patients treated non-operatively developed local recurrence at a median time of 11 months. Three of these patients also recurred distantly. All patients underwent surgical salvage. Compared to a control group of 57 patients treated with CRT and TME who developed pCR, the non-operatively managed patients had a statistically higher rate of LR (2-year = 21% vs 0%). However, 2-year distant recurrence, DFS and OS were favorable and not different between groups.

A recently reported early prospective non-operative study in cT2-4/N0-2 distal rectal adenocarcinoma by Habr-Gama et al. [70] included strict criteria to define cCR which also incorporated positron emission tomography (PET) scans. Notably, these investigators dichotomized cCR into early (at 10 weeks post-CRT) and sustained (at 12 months post-CRT) responder groups. Additionally, these patients also received extended CRT to 54 Gy and 6-cycles of bolus 5-FU after CRT prior to their first assessment of response. Of 70 patients, 68% developed an early cCR and 57% had a sustained cCR. During the first 12 months, there were 8 local recurrences. At a median follow-up of 53 months, 4 patients (10%) with a sustained cCR developed LR. There were 5 distant recurrences in the sustained cCR group. The 3-year DFS and OS were 75% and 94%, respectively [70]. Based on these outcomes, >50% of patients with a cCR by 10 weeks sustain their response over the ensuing year indicating both the excellent outcomes and importance of close surveillance for surgical salvage.

There are numerous challenges when considering non-operative management, the primary one being which patients to offer a "wait-and-see" approach. They could be older and unable to undergo surgery, unwilling to have surgery, present with early stage disease and prefer to avoid surgery and those with locally advanced disease undergoing neoadjuvant CRT who experience a cCR. The studies presented here and in the literature have differing inclusion criteria, neoadjuvant therapy parameters, adjuvant therapy, and importantly, differing definitions of cCR. This latter component is most important when identifying patients who may benefit from non-operative management. Radiologic methods such as endorectal ultrasound and MRI have improved assessment of disease both pre- and post-therapy in rectal cancer. The prospective studies by Maas et al. and Habr-Gama et al. included stringent criteria to define cCR and monitoring during follow-up which is critical for pursuing non-operative management. Another important parameter is the duration from CRT to surgery. A multicenter prospective trial initiated by The Timing of Rectal

Cancer Response to Chemoradiation Constortium demonstrated a higher-rate of pCR (25% vs 18%) if surgery was delayed to ~8 versus 6 weeks post-CRT and additional chemotherapy was administered [71]. The addition of further chemotherapy after CRT is routine in many non-operative trials and is reflected in the increasing use of induction chemotherapy for locally advanced disease [72]. Treatment of recurrent tumors after non-operative management is critically important when considering this approach. A recent report revealed that salvage therapy for either early or late LR after a cCR and no surgery resulted in a 5-year local recurrence-free survival of 94% [73]. When including all patients with a cCR by 8 weeks post-cRT (n = 90), the organ preservation rate at a median follow-up of 60 months was a respectable 78%.

Radiotherapy, particularly when combined with concurrent chemotherapy, has significant and lasting side effects. In an analogous effort to non-operative management, there is interest in identifying patients who may not require CRT after undergoing a course of induction chemotherapy. Investigators at MSKCC performed a pilot study of induction chemotherapy without routine radiotherapy in 32 patients with cT3N0-2 mid-rectal tumors. Patients were initially treated with 4 cycles of FOLFOX combined with bevacizumab followed by an additional 2 cycles of FOLFOX. Upon restaging with proctoscopy, endorectal ultrasound and MRI, any patients with progression or no evidence of response received 5-FU based CRT. From the original cohort of 32 patients, only 2 received neoadjuvant CRT due to intolerance of the induction chemotherapy. At the time of TME, 25% of patients were found to have a pCR. One patient received post-operative RT for a close circumferential margin. At a median follow-up of 54 months, there have been no local recurrences and only 4 (12.5%) distant metastases. The 4-year DFS and OS rates were both ~92% [74]. Based on these results, a multicenter, phase III randomized control trial called the Preoperative Radiation or Selective Preoperative Radiation and Evaluation before Chemotherapy and TME (PROSPECT) is now open and currently accruing patients.

Finally, there are patients who may benefit from more aggressive management, in particular those at high-risk for micrometastatic disease. In these patients, administering chemotherapy prior to pre-operative CRT could potentially improve distant control. The use of total neoadjuvant therapy, i.e. giving induction chemotherapy and CRT prior to surgery, has been evaluated in two prospective studies. A Spanish study randomized 108 patients with locally advanced rectal cancer displaying high-risk features on MRI (threatened/involved CRM, distal cT3, resectable cT4, and any cT3N+) to 4 cycles of CAPOX chemotherapy either prior to neoadjuvant CAPOX-based CRT and TME or post-operatively. The primary endpoint of pCR was the same between groups (13% adjuvant vs 14% induction); however, there was significantly more Grade 3–4 toxicity during adjuvant chemotherapy (19% vs 54%, $p = 0.0004$) leading to much fewer patients completing all 4 cycles of CAPOX (57% vs 94%, $p = 0.0001$) [75]. A Phase II study from the United Kingdom explored induction CAPOX chemotherapy in a similar cohort of 105 high-risk rectal cancer identified by MRI and treated with neoadjuvant capecitabine-based CRT and TME followed by adjuvant CAPOX chemotherapy (Trial NCT00220051). The primary

endpoint of pCR was slightly higher at 20% and serious adverse events were similar during both induction and adjuvant chemotherapy, although there were 9 reported cardiopulmonary events resulting in 4 deaths during neoadjuvant chemotherapy resulting in stricter exclusion criteria for patients with pre-existing cardiac morbidity [76]. From these studies, it appears that induction chemotherapy is well tolerated, perhaps better than adjuvant treatment and further studies are underway in an effort to explore its impact on long-term oncologic outcomes.

Intensity Modulated Radiation Therapy in Rectal Cancer

Intensity modulated radiation therapy or IMRT is a technique in Radiation Oncology using multiple radiation beams to create a conformal dose distribution. In theory, therapy plans can be designed to minimize radiation dose to normal tissues and reduce side effects. IMRT differs from standard pelvic radiation plans which use 3–4 external beams and wedges as there are often 5 or more beams employed with a lengthened treatment time. Application of IMRT to most pelvic malignancies such as anal, cervical and prostate has demonstrated significantly reduced adverse events, particularly acute gastrointestinal toxicity [77–79]. The use of IMRT in locally advanced rectal cancer has been pursued in a similar manner to reduce gastrointestinal toxicity. Dosimetric planning studies comparing three-dimensional conformal radiation therapy (3DCRT) to IMRT have predicted decreased radiation deposited in dose-limiting structures like the small bowel, which is thought to be the primary cause of acute and long-term GI toxicity [80, 81]. Reducing acute GI toxicity may also prove beneficial by decreasing treatment delays, which has been shown to be detrimental in local control for rectal cancer [82].

Numerous retrospective studies and early phase I and II prospective trials have investigated GI toxicity and cancer-specific outcomes in locally advanced rectal cancer treated with concurrent chemoradiation using IMRT. Three retrospective comparisons of 3DCRT to IMRT used in mostly neoadjuvant CRT of locally advanced rectal cancer revealed a significant absolute decrease in acute Grade 2–3 GI toxicity of approximately 30% [83–85]. This is primarily due to a reduction in diarrhea frequency. An additional multi-institutional retrospective study by Jabbour et al. demonstrated a significant reduction in treatment breaks and emergency room visits in patients treated with IMRT [86]. These studies also show no difference in pathologic complete response rates with more conformal radiotherapy (~20%). The findings from these reports are summarized in Table 21.5.

A multi-institutional prospective Phase II trial studied the use of neoadjuvant IMRT-based CRT in cT3–T4, N0–N2, M0 rectal adenocarcinoma of the low-mid rectum. This study, RTOG 0822, had a primary endpoint of acute pre-operative GI toxicity ≥ Grade 2 using the CRT arm of RTOG 0247 as the historical comparison [87]. Treatment consisted of concurrent CAPOX with pelvic IMRT to a total dose of 45 Gy in 25 fractions followed by a 3D conformal boost of 5.4 Gy in 3 fractions to the primary disease. The results, only reported in abstract form, demonstrated a

Table 21.5 Retrospective experience of the use of IMRT in chemoradiotherapy for locally advanced rectal cancer

Study	Patients	Acute adverse events		pCR rates	LR rates
Yang et al. [84]	98 IMRT 79 3DCRT (8% adjuvant)	Grade 2+ Diarrhea (32% 3DCRT vs 11% IMRT) – *SS*	GI toxicity significantly associated with female sex and bowel	NR	NR
Jabbour et al. [86]	30 IMRT 56 3DCRT (0% adjuvant)	Grade 3+ Diarrhea (9% 3DCRT vs 1% IMRT) – *NS*	Fewer treatment breaks (20% 3DCRT vs 0% IMRT) – *SS* ↓ ER visits (14% 3DCRT vs 2% IMRT) – *SS*	21% 3DCRT vs 20% IMRT (*NS*)	7% 3DCRT vs 6.7% IMRT (*NS*)
Parekh et al. [85]	20 IMRT 28 3DCRT (0% adjuvant)	Grade 2–3 GI (3DCRT 60.7% vs 30%) – *SS*	Grade 2–3 diarrhea (42.8% 3DCRT vs 10% IMRT) – *SS*	17% 3DCRT vs 21% IMRT (*NS*)	NR
Samuelian et al. [83]	31 IMRT 61 3DCRT (12% adjuvant)	Grade 2–3 GI (3DCRT 62% vs 32%) – *SS*	Grade 2–3 diarrhea (3DCRT 48% vs 23% IMRT) – *SS* Grade 2–3 enteritis (3DCRT 30% vs 10% IMRT) – *SS*	28% 3DCRT vs 19% IMRT (*NS*)	NR

pCR pathologic complete response; *LR* local recurrence; *IMRT* Intensity modulated radiation therapy; *3DCRT* 3-dimensional conformal radiation therapy; *GI* gastrointestinal; *SS* statistical significant; *NS* non-significant; *NR* not reported

rate of pre-operative Grade 2 GI toxicity not statistically different from the historical control (51% vs. 58% in RTOG 0247). Notably there was no decrement in pCR (14.7%) or 4-year LRR (7.4%) [88]. A similar prospective Phase II trial was performed in Spain, but utilized a hypofractionated radiation regimen (47.5 Gy in 19–20 fractions) and a lower dose of oxaliplatin (50 mg/m^2/wk) [89]. An increased rate of Grade 3+ proctitis was found with the higher dose per fraction (2.37 Gy). The overall rate of Grade 3+ diarrhea was 9% with a similar pCR rate to RTOG 0822 at 13% overall. Additional moderately-sized prospective trials of neoadjuvant IMRT in rectal cancer are summarized in Table 21.6.

These results contrast with the findings of the analogous IMRT trial in anal cancer, RTOG 0529. In this Phase II study, cT2–T4, N0–N3, M0 anal cancer patients were treated with concurrent 5-FU and mitomycin-C (MMC) chemoradiation using IMRT [79]. The primary endpoint was a 15% or more reduction in combined acute Grade ≥2 GI or genitourinary (GU) toxicity when compared with the conventional CRT arm of RTOG 9811 (compared induction 5-FU and cisplatin followed by concurrent 5-FU and cisplatin CRT to standard 5-FU/MMC CRT). Although the primary endpoint was not met (77% overall acute grade 2+ GI/GU in both trials), there was a statistically significant decrease in Grade ≥2 hematologic (85% → 73%), Grade ≥3 GI/GU (37% → 21%), and Grade ≥3 radiation dermatitis (49% → 23%)

Table 21.6 Prospective trials of neoadjuvant IMRT in locally advanced rectal cancer

Study	Patients	IMRT Dose/ Fx	Chemo	Toxicity	pCR	Outcomes
RTOG 0822 [87]	79	45 Gy / 25 + CB of 5.4 Gy / 3	Capecitabine Oxaliplatin	Grade 2+ GI = 51%	14.7%	4-year LRF = 7.4%
Arbea et al. [89]	100	47.5 Gy / 19–20	Capecitabine Oxaliplatin	Grade 3+ diarrhea = 9% Grade 3+ proctitis = 4%	13%	6-year DFS = 84.2%
Engels et al. [165]	108	46 Gy / 23 + SIB to 55.2 Gy	None	Grade 3+ GI = 9%	8%	5-year LC = 97%
Hernando-Requejo et al. [166]	74	46 Gy / 23 + SIB to 57.5 Gy	Capecitabine	Grade 3+ GI = 9.5%	30.6%	3-year DFS = 85.9%

Fx fraction; *Gy* Gray; *CB* concomitant boost; *SIB* simultaneous integrated boost; *GI* gastrointestinal; *pCR* pathologic complete response; *LRF* locoregional failure; *DFS* disease free survival; *LC* local control

toxicities. This led to IMRT becoming the *de facto* standard of care radiation modality for anal cancer.

One potential confounder of the rectal cancer IMRT trial (RTOG 0822) and the Spanish trial was the use of oxaliplatin in addition to 5-FU during concurrent chemoradiation. As described previously, three of the 4 large randomized controlled trials recently reported that examined the addition of oxaliplatin to standard 5-FU or capecitabine-based neoadjuvant CRT demonstrated significantly more Grade ≥3 toxicity with the addition of oxaliplatin. Given these toxicity outcomes (additional oxaliplatin), the design of RTOG 0822 may have obscured any potential reduction in toxicity with IMRT.

The American College of Radiology Appropriateness Criteria® for resectable rectal cancer states that IMRT decreases toxicity and should be considered for patients requiring large treatment volumes (inguinal lymph node irradiation or post-operative) [90]. The consensus is that any other patients receiving IMRT should be enrolled on a clinical trial given the difficulty in designing, planning and delivering IMRT as revealed in the anal cancer RTOG 0529 trial which demonstrated a significant number of plan revisions after peer review [79]. Notably, a randomized double-blind pilot study for IMRT rectal cancer volume delineation revealed that use of a standardized atlas significantly improved inter-physician contours [91]. The 2015 NCCN Guidelines for rectal cancer also state that IMRT should only be utilized in certain situations such as a clinical trial or re-irradiation settings for recurrent disease (www.NCCN.org). At our institution, we routinely utilize IMRT in treating most cases of locally advanced rectal cancer in the neoadjuvant setting given our extensive prior experience. Given the findings of increased toxicity with simultaneous integrated boosts >50 Gy with IMRT, but the established high pCR rates with a boost to the gross disease [92], we incorporate a simultane-

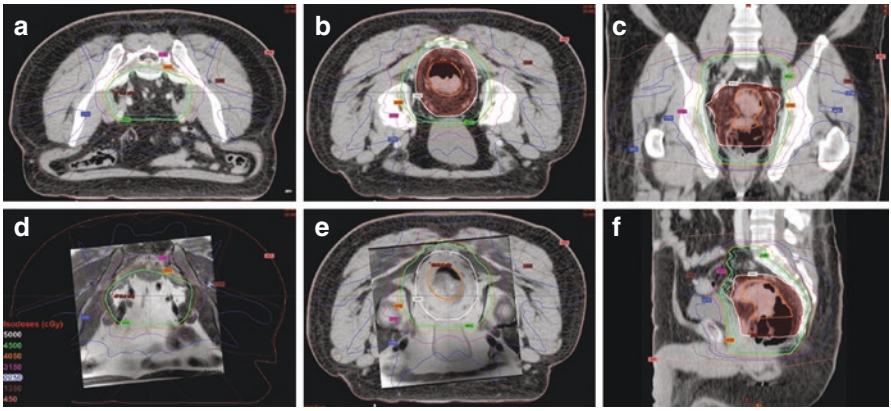

Fig. 21.1 Treatment plan for neoadjuvant CRT of Stage II/III disease. In addition to the gross tumor volume (GTV) including suspicious or involved lymph nodes, the CTV A volume is electively treated. The GTV of the primary tumor is in orange and encompasses the entire rectum at the levels of disease. The planning target volume for the primary tumor is given in red. The total doses are 4500 cGy to the elective volumes (CTV A) and a simultaneous integrated boost of an additional 5 Gy to the gross disease. (**a**) Superior portion of treatment including the fused MRI (**d**). (**b**) Inferior portion of the treatment including the fused MRI (**e**). (**c** and **d**) Coronal and sagittal views of the treatment volume. The isodose lines are depicted in various colors with the legend at the bottom of the image

ous integrated boost to 50 Gy. If electing to employ IMRT, we recommend reviewing the RTOG consensus panel contouring atlas [93] and the dose constraints followed in RTOG 0529. (Note the example provided in Fig. 21.1 of an IMRT preoperative rectal cancer plan.)

Radiation Therapy Planning in Rectal Cancer

Radiation planning for rectal cancer is a multidisciplinary effort involving the Radiation Oncologist, Colorectal Surgeon, Medical Oncologist, Radiologist, and Medical Physicist. It is ultimately the responsibility of the Radiation Oncologist to define the treatment volume including gross tumor and tissues at risk as well as the normal tissue structures to which the radiation dose should be minimized. Treatment planning is critical as it may impact outcomes. Input from the surgeon's evaluation under endoscopy and rigid sigmoidoscopy aids in defining the extent of the primary tumor including the distance from the anal verge and the dentate line as well as mesorectal nodal involvement. Diagnostic CT, MRI and PET scans help identify and delineate the primary tumor and nodal disease as well as any distant metastases. Combined modality therapy, selection of chemotherapeutic agents and addition of induction chemotherapy influence radiation scheduling and the need for further imaging prior to radiotherapy planning. All of these factors determine the radiation

dose, RT field extent and RT modality employed (3DCRT vs IMRT or short-course vs long course).

Patients are commonly simulated in the prone position on a rigid board to help displace small bowel out of the pelvis. Exceptions may include young males requiring a block over the genitalia to reduce the dose to the reproductive structures or treatment with IMRT. The patient is often immobilized in an aquaplast mold or other device in order to ensure proper treatment setup and reproducibility during each fraction. Oral contrast can be administered to help demarcate the small bowel. Our institution avoids oral contrast as it may exacerbate underlying GI symptoms. We employ intravenous contrast to identify the bowel wall and pelvic vessels. A radiopaque fiducial marker should be placed at the anus for identification later. For high tumors near the peritoneal reflection, a radiopaque catheter can be used to demarcate the anal canal. The patient should be simulated with either the bladder full or empty with instruction to have the same bladder status during every treatment. We use a full bladder protocol and perform weekly cone beam CT scans on our treatment machines to assess variation in bladder filling.

Radiation therapy treatment planning involves identification of 3 different treatment volumes: the gross tumor volume (GTV), clinical treatment volume (CTV) and planning target volume (PTV). The GTV includes the primary tumor and any nodal disease. The CTV includes the GTV with an expansion to encompass microscopic extension as well as any other areas at risk for microscopic disease. The PTV includes the CTV with a small margin (3–5 mm) for setup errors and organ motion. With the advent of CT-based simulation providing clearer anatomical information and more frequent application of IMRT, specific guidelines were developed to ensure coverage of all areas at risk and normalize treatment across centers. The RTOG consensus contouring atlas for anorectal cancer provides detailed descriptions of the elective regions to cover divided into 3 CTVs based upon disease stage and location [93]. Application of the atlas has been shown to improve agreement in treatment volumes between Radiation Oncologists and theoretically increase tumor control probability and reduce toxicity to the small intestine [91, 94]. Detailed definitions of the prescribed treatment volumes are beyond the scope of this chapter and the interested reader should review the RTOG atlas for further information. An example of a neoadjuvant IMRT treatment plan for a case of LARC is provided in Fig. 21.1.

The PTV including the CTVs and gross disease is typically treated to 45 Gy in 25 fractions. A boost dose is administered to the primary tumor including the surrounding mesorectum and the presacral space at the involved levels with a 2 cm expansion including any gross nodal disease. These expansions tend to cover any potential rectal motion during treatment although non-uniform margins have been suggested [95, 96]. The boost is either performed with an additional 3 fractions of treatment totaling 5.4 Gy or as a simultaneous integrated boost during IMRT where the fraction size is larger (2 Gy vs 1.8 Gy) for the boost volume. The latter accelerates the overall treatment course. Some have also suggested a higher total boost

dose to 54–56 Gy for T4 disease as is done in anal cancer [97]. However, this is not routinely practiced as it was not included in the pre-operative CRT trials.

In addition to the gross tumor and regions at risk for microscopic disease, the Radiation Oncologist must identify normal tissue structures to avoid or limit the dose. These are often denoted as "organs at risk" (OARs). For rectal cancer, these include the small bowel, large bowel, bladder, femoral heads and external genitalia including the vagina for women. The RTOG developed consensus guidelines for contouring normal tissues in the pelvis which is available for reference [98]. An additional structure that is often included within the GTV of rectal cancer patients is the lumbosacral plexus. There is a risk of lumbosacral plexopathy secondary to radiation, but the actual frequency of this problem is unknown. A standardized contouring atlas is available [99] and while not routinely utilized during primary therapy, it may be of use during cases of re-irradiation when the cumulative dose to these nerves is of concern. Dose constraints for OARs are often institution-dependent. Suggested constraints are described for IMRT in the RTOG 0822 trial and by QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) for 3DCRT [87, 100].

Brachytherapy and Intraoperative Radiation Therapy

One of the potential goals of IMRT is to increase the radiation dose while sparing surrounding tissues so as to improve tumor control, although this has yet to be definitively demonstrated. Another radiation modality that permits dose-escalation is brachytherapy which is advantageous due to the rapid dose fall-off from the source to the adjacent normal tissues. In addition, brachytherapy for rectal cancer is often applied in fewer higher dose fractions which may provide an additional radiobiological advantage. In rectal cancer, brachytherapy has been used in a number of contexts including treatment of early stage disease, as an adjunct to external beam therapy in unresectable or advanced disease and for recurrent disease. Endorectal brachytherapy (EBT) was first introduced in the 1940's and later pioneered by J. Papillion in France. Using a 50 kV X-ray tube, the "Papillion" technique applies contact X-ray therapy to 20–30 Gy over 4 applications occasionally supplemented with adjuvant interstitial iridium-192 brachytherapy to early stage T1 and T2 exophytic rectal cancer. In their original report of 312 patients, the 5-year disease free survival was 74% with a crude local failure rate of 4.5% by 5 years [101]. The toxicity rates and performance outcomes were excellent with only 10% of patients experiencing acute proctitis and normal anal sphincter function in 96% of patients alive at 5-years. The application of staging by endorectal ultrasound in a modern series utilizing the Papillion technique reported by Gerard et al. demonstrated a 4-year freedom from locoregional failure >90% for T1N0 (100% for uT1N0) and polypoid lesions, but only ~60% for T2N0 lesions [102].

Investigators at the University of Minnesota retrospectively examined 149 older patients (median age 74) with uT1N0 and uT2N0 rectal cancer treated with 50 kV

contact brachytherapy to a median dose 90 Gy and no further therapy [103]. They found a 5-year local failure rate of 23% and 5-year DFS of 74% with no differences based on stage (uT1 vs uT2). With the inclusion of salvage therapy, the 5-year DFS rate was 87%. The addition of local excision to interstitial brachytherapy with iridium-192 catheters resulted in no improvement for T1 and T2 rectal cancer [104]. A long-term retrospective study from the Mayo Clinic revealed a 10-year local control rate of 76% and overall survival of 42% in a mixed group of 35 Stage II-III rectal cancer patients treated with curative intent using 50-kV X-ray EBT and occasionally adjuvant surgery, chemotherapy, or external radiation [105]. In summary, EBT alone for early stage, lymph node negative rectal cancer provides good local control, but should be reserved for elderly, medically unfit patients, or those refusing surgery or colostomy. The International Society of Geriatric Oncology has identified EBT for T1 and T2 rectal cancer for elderly patients as a research priority in Radiation Oncology [106]. In summary, although this technique and its variants have been in use for over 80 years there are few centers around the world which have persisted with this technique. The overall numbers for such treatment are small and there is the development of a series of competing surgical techniques which have been well tolerated by patients such as Trans Endoscopic Microsurgery (TEMS) and Trans Anal Minimally Invasive Surgery (TAMIS) covered elsewhere in this book (Chap. 9, Part IV).

While the standard of care for locally advanced rectal cancer is preoperative chemoradiation using external beam radiotherapy, there are studies demonstrating good outcomes with neoadjuvant high-dose rate EBT (HDR-EBT). The largest prospective trial reported is from McGill University and explored the use of neoadjuvant HDR-EBT in resectable locally advanced rectal cancer [107, 108]. In their update, 100 patients were treated with HDR-EBT (6.5 Gy × 4) using CT-guided planning to encompass the primary tumor and MRI-identified mesorectal lymph nodes. The pCR rate of the primary tumor was 29% and the majority of patients with persistent nodal disease (28%) received post-operative RT. At a median follow-up of 60 months, the 5-year LRR was 5% with a DFS of 65%. While trials of EBT for locally advanced rectal cancer investigate an RT modality with potentially lower toxicity than EBRT, brachytherapy alone cannot address nodal disease prohibiting its use in T2 and early T3 cases with a risk of nodal disease in 20–30% of cases. The downside of omitting CRT is highlighted in the McGill study where there was a 68% systemic relapse rate in patients with pN+ after surgery.

The OPERA trial NCT 02505750 has been initiated as a randomized study on cT2, cT3a-b tumors less than 5 cm comparing different techniques of RT boost after neoadjuvant CRT either as EBRT (9 Gy/5 Fractions) or contact x-ray brachytherapy (CXB) (90 Gy/3 Fractions) with an endpoint of organ preservation (at 3 years) without non-salvageable local pelvic recurrence. This trial is particularly directed at elderly unfit patients. This study will be of interest to determine whether the addition of an endocavitary boost with CXB after a standard CRT treatment will increase the chances of rectal/anal preservation.

Intraoperative radiation therapy (IORT) involves delivery of radiotherapy at the time of operation. In rectal cancer, IORT has been employed for primary unresect-

able disease, recurrent disease and as an adjunct to standard CRT. There are 2 primary radiation modalities for IORT: intraoperative electron radiation therapy (IOERT) and high-dose rate brachytherapy (HDR-IORT). Detailed descriptions of both techniques can be found elsewhere [109, 110]. Briefly, IOERT often utilizes a shielded compact linear accelerator generating electron energies ranging from 4 to 18 MeV equating to a penetration depth of ~1–5.5 cm with the radiation delivered directly to the operative bed utilizing variously designed cone applicators. HDR-IORT involves a mobile remote-controlled after loader with an iridium-192 source that travels along a cable to a flexible applicator. Each technique has advantages and disadvantages secondary to the type of radiation and instrumentation. Treatment with IOERT can encompass a significant range of residual disease beyond the surgical margins due to the deeper tissue penetration of the electrons. HDR-IORT has a superficial penetration of 0.5–1 cm, but can conform to curved operative beds to which the cone applicator of IOERT cannot be easily applied. Treatment time with IOERT is shorter than HDR-IORT which can often take as long as 45 min depending upon the size of the treatment area. As there have been no randomized control trials of IORT, the remainder of this section will focus on large cooperative group or single-intuitional studies.

The RTOG performed a Phase I/II study of IORT in 42 rectal cancer patients with residual post-operative, unresectable, or recurrent disease. Patients received a median of 16.5 Gy using IOERT with some patients receiving post-op RT. The overall 2-year LRR control rate was 38% with the notable findings of significantly better LRR control and OS in those patients with no or microscopic residual disease post-operatively [111]. Incorporation of IORT in the treatment of recurrent rectal cancer has been performed successfully at a number of centers. When combined with EBRT +/− chemotherapy and salvage surgery, IORT reasonably improves both overall and disease-free survival [110]. The largest study employing IORT is from the Mayo Clinic where they reported the outcomes of 607 cases of recurrent colorectal cancer (70% rectal primary) managed with surgical resection and IOERT [112]. The majority of these patients (96%) also received EBRT (median dose = 45.5 Gy) with concurrent 5-FU (81%) while cases of re-irradiation (45%) received a lower median dose of 27.5 Gy. The dose of IOERT depended upon the resection status, ranging from 12.5 (R0)–20 Gy (R2). Overall survival was 30% over 5-years with chemotherapy naïve patients and negative surgical margins predicting a better outcome. The 5-year rate of LR was 28% and more common in partially resected (32% vs 21%) or previously irradiated (37% vs 22%) patients. The most common toxicity related to IOERT was wound complications (7%). Fifteen-percent of patients experienced peripheral neuropathy which was more common with IOERT doses >12.5 Gy. An older study from MGH [113], reported similar 5-year survival rates, but a worse local control rate (35%) likely due to differences in adjuvant radiation and chemotherapy.

Both MSKCC and MDACC have reported retrospective studies of HDR-IORT in recurrent rectal cancer patients treated with similar adjuvant therapy (EBRT and 5-FU based chemotherapy) to those with IOERT. The median dose in each study was 15 and 12.5 Gy, respectively. The 5-year local control and overall survival rates

in the MSKCC series of 212 recurrent rectal cancer patients were 38% and 45%, respectively [114]. The MDACC study included 70 recurrent patients and reported a slightly higher 5-year LC rate of 56% and a similar OS of 56% [115]. In summary, IORT for rectal cancer has the best outcomes after gross total resection of tumor. The benefit of IORT as an adjunct to EBRT is unclear. However, the application of IORT to rectal cancer continues to advance with new techniques of orthovoltage X-ray (200–250 kVp) [116] and IORT photon (50 kV) systems [117]. Given the improved outcomes with neoadjuvant CRT for locally advanced rectal cancer, IORT is now primarily used for clinical or radiographic unresectable disease or locally recurrent disease undergoing resection.

Radiation Therapy in the Unresectable or Metastatic Setting

Of the nearly 40,000 cases of rectal cancers that will be diagnosed in 2015, approximately 20% will have distant disease at presentation [118]. Additionally around 5% of non-metastatic cases will also be unresectable by standard surgery due to involvement of adjacent critical organs. In the case of unresectable rectal cancer, CRT is the primary treatment modality with the goal of downstaging the tumor in order to facilitate surgical resection. Guidelines for the application of radiotherapy in metastatic rectal cancer are sparse. Options range from standard therapy to the primary tumor to supportive care with palliative radiation to painful or obstructive lesions. The American College of Radiology has defined criteria for radiation therapy in metastatic rectal cancer which often follows systemic chemotherapy in patients with limited metastatic disease [119]. There are no Phase III trials which address the therapeutic options given the variability of presentation, leaving the optimal sequencing of CT, RT and surgery unresolved. This section will focus on the addition of radiotherapy to surgery and chemotherapy for the treatment of both unresectable and resectable metastatic disease. Detailed discussions of therapy for metastatic rectal cancer are presented in section.

There are limited studies available in the literature that focus on unresectable rectal cancer. Most are single institution retrospective studies. In one of the largest of these, investigators from the Mayo Clinic reported outcomes of combined modality therapy for unresectable colorectal cancer patients. Nearly three-quarters of the patients were primary rectal adenocarcinomas and approximately 10% had M1 disease at presentation. Patients were administered either pre- or post-operative RT, most often with concurrent 5-FU (90%). During surgical resection, IORT was delivered to all patients at a median dose of 12.5 Gy. Adjuvant chemotherapy was administered in 45% of patients. After a median follow-up of 3.7 years, the 3-year freedom from LR was 90% [120]. The corresponding 3-year DFS and OS were 52% and 61%, respectively. Pre-operative RT and adjuvant chemotherapy were found to be predictors of improved OS. Pooling their data with the Catharina Hospital Eindhoven, almost three-quarters of cases were able to undergo an R0 resection with both LR and metastatic disease occurring more frequently in those where an

R0 resection could not be achieved. The use of preoperative CRT enhanced the likelihood of an R0 resection [121].

The addition of chemotherapy to RT in the neoadjuvant setting for unresectable T4 or recurrent rectal cancer was tested in a randomized control trial. In this study reported by Braendengen et al., 207 patients were randomized to either RT alone or CRT with concurrent bolus 5-FU and leucovorin [122]. A radiation dose of 46 Gy was delivered to areas in the pelvis at risk with an additional 2 doses to the primary tumor and gross disease for a total of 50 Gy over 25 treatments using standard 3DCRT techniques. Surgery was attempted 5–8 weeks after RT. All CRT patients received adjuvant 5-FU chemotherapy while those in the RT alone cohort received CT for Stage III or higher disease. Significantly more patients in the CRT cohort underwent a lower anterior resection (47% vs 29%, respectively) and achieved sphincter preservation if resected (53% vs 36%, respectively). This group also underwent more R0 resections (84% vs 68%, respectively, and demonstrated a pCR (16% vs 7%, respectively). Local control at 5-years (82% vs 67%, respectively) and cancer-specific survival (72% vs 55%, respectively) were both significantly better after CRT with a trend for advantage in OS. From these studies, it is apparent that patients with unresectable locally advanced disease benefit from combined modality therapy including CRT.

Metastatic rectal cancer is most likely divided into two subgroups with differing prognoses based upon the underlying tumor biology. Oligometastatic (OM) disease, first proposed by Hellman and Weichselbaum in 1995, is potentially curable due to limited spread and underlying favorable biology [123, 124]. Patients with oligometastatic disease are typically characterized as having 5 or fewer metastatic sites of disease involving 3 or fewer organ sites. The primary sites of distant metastases from rectal cancer (besides the lymph nodes) are the liver and the lung. Treatment of individual hepatic or pulmonary metastases in patients with limited metastatic disease has been shown to result in 5-year OS rates in excess of 30% [125]. Stereotactic body radiotherapy (SBRT) has been proposed as a possible curable RT modality for OM disease in a number of cancer subtypes including colorectal [126–129].

SBRT involves the use of high-dose radiation delivered as limited fractions (1–5) often using image-guided radiation therapy techniques and conformal IMRT planning. Phase II trials of SBRT in hepatic, pulmonary and spinal metastases have been performed often with local control as the primary endpoint. Treatment of liver metastases with SBRT to a total dose of 60 Gy in 3 fractions resulted in local control at 2-years greater than 90% [130]. Overall survival at 2-years was 30% and found to be significantly better in patients with colorectal primaries. A similar Phase I/II trial was performed in patients with 1–3 pulmonary metastases including nearly 25% from colorectal primaries. Patients were again treated with a maximum of 60 Gy over 3 fractions to each lesion. Treatment-related toxicity of Grade 3 (none were higher) was 8% with a 3% rate of symptomatic pneumonitis. The 2-year local control was again excellent at greater than 95%. The 2-year OS was a respectable 39% for the 38 enrolled patients [131].

Although not a common site for rectal cancer metastases, SBRT (27–30 Gy in 3 fractions) for symptomatic, mechanically stable (surgery not required) spinal metas-

tases resulted in a significant reduction in pain and opioid usage within 6 months post-treatment [132]. In addition, the 2-year progression-free survival was 72% in 166 treated lesions. In patients with clearly defined OM disease (≤3 sites), a retrospective review from the UK of lesions (38% colorectal origin) treated with SBRT (max dose 40 Gy) in multiple organ sites demonstrated a 2-year OS of 63% [133]. These outcomes appear better than the 5-year OS of approximately 10% for Stage IV rectal cancer.

There is only one reported Phase II trial of SBRT specifically delivered to metastases from colorectal cancer. In a study by investigators in Denmark, 64 patients with Stage IV rectal cancer received SBRT to 1–4 inoperable metastases after radical surgical resection of their primary tumor. The majority of the treated sites involved either the liver or lung. SBRT was delivered over 3 fractions to a total dose of 45 Gy [134]. The 2-year LC to all sites was 86% with an OS of 38%. After a median follow-up of 4.3 years, the 4-year OS was 13% which differs little from standard survival statistics for Stage IV rectal cancer. This outcome may have been due to the inoperable nature of these metastatic sites selecting for worse underlying biology. Slightly better 5-year OS was observed in a Korean retrospective study where the median SBRT dose to colorectal cancer metastases was higher at 48 Gy indicating possibly better tumor control [135].

Treatment of the primary tumor in Stage IV disease regardless the number of metastases is an important consideration due to existing or potential local symptoms. The primary treatment for Stage IV rectal cancer is chemotherapy. If the metastatic disease is limited, the primary tumor can be addressed surgically. Metastasectomies of distant lesions involving the liver and lung can also be performed. In many cases, the American College of Radiology recommends neoadjuvant treatment with either concurrent CRT or short-course RT, unless the case is palliative [119]. A Dutch Phase II trial examined short course RT (5 Gy × 5) followed by treatment with bevacizumab, oxaliplatin, and capecitabine in 50 patients with metastatic rectal cancer to either the liver or lung [136]. All lesions had to be technically resectable. In 72% of patients, the primary tumor and metastatic lesions were successfully managed with R0 resections after RT and chemotherapy. The primary tumor was resected in 90% of patients with a pCR of 26%. Local control was maintained in the pelvis for all but 2 patients after a median follow-up of 32 months. The 2-year recurrence rate and OS were 64% and 80%, respectively. A retrospective series of 26 rectal cancer patients with liver oligometastases treated with long-course CRT demonstrated better 2-year LC of 66% and similar OS of 70% [137]. From this limited data, it appears that Stage IV rectal cancer can receive curative treatment with some success using either short-course RT or long-course CRT.

Radiation plays a critically important role in late-stage cancer as a palliative measure. In rectal cancer, symptomatic metastatic sites involving multiple organ systems can be addressed with palliative radiotherapy alone. The radiation doses can range from a single treatment of 8 Gy to 30 Gy or more over 10 fractions or greater. Rectal cancer is unique as the primary tumor or pelvic recurrences can cause significant symptoms including pain, bowel obstruction, and bleeding. Using

radiation administered by various regimens has been shown to palliate symptoms in up to 80% of patients with metastatic disease [138]. It is the role of the Radiation Oncologist in consultation with the multidisciplinary team to determine when a patient may benefit from a course of radiation and over what duration to administer it balancing treatment outcomes, side effects, and goals of care.

Role of Radiation Therapy in Recurrent Rectal Cancer

Modern neoadjuvant chemoradiotherapy or short-course hypofractionated radiation alone coupled with TME results in local recurrence rates less than 10% [10, 13, 19, 64]. Pelvic recurrences alone still occur and often lead to debilitating symptoms due to local progression causing pain, bowel obstruction, or hemorrhage. Additionally, the prognosis after locoregional recurrence of rectal cancer is dismal with a five-year overall survival rate <5% [139]. Surgery is the only potentially curative modality for recurrent disease if gross total resection is achieved. Improvements in surgical techniques have increased survival rates beyond historical reports [140]. However, the surgical approach can be complex if there is involvement of pelvic sidewalls and/or lymph nodes and is therefore often coupled with radiation and chemotherapy [141]. If a patient is radiation naïve and has no evidence of distant metastases, the standard course of preoperative chemoradiation is recommended to both improve prognosis and hopefully downstage the tumor to aid surgical resection. Further, preoperative radiation has been shown to improve local control over surgery alone, but has not shown a benefit in OS [142]. The challenge for adjuvant treatment arises in the previously irradiated patient. There are a number of radiation techniques applied for these patients including IORT, brachytherapy, and hyperfractionated radiation therapy (see above section "Radiation Therapy in the Unresectable or Metastatic Setting" of this chapter).

Intraoperative radiation therapy is able to directly deliver treatment to areas of concern at the time of operation, but cannot easily or safely target large areas. If a patient with recurrent disease has not received prior radiation therapy, they should receive neoadjuvant chemoradiation per recommended guidelines [143]. For more advanced cases of recurrent rectal cancer invading into bone or adjacent organs, the inclusion of induction chemotherapy prior to radiation to assess therapeutic response and improve resectability is finding increasing use. In the case of reirradiation, additional EBRT can be delivered either conventionally or by a hyperfractionated regimen. Radiobiologically, hyperfractionated radiation may provide an advantage by decreasing late toxic effects due to normal tissue damage while still proving cytotoxic to cancer cells, particularly when given multiple times a day to account for the lower dose per fraction.

Investigators at the University of Kentucky recently reported their long-term experience re-irradiating recurrent rectal cancer with both conventional RT (30.6 Gy/17 fractions once daily) and hyperfractionated (30 Gy/25 fractions twice daily) with concurrent 5-FU and a boost of 6–20 Gy to limited tumor volume [144].

They did not report local control. The 5-year OS was 19% which was statistically improved if patients underwent surgery, had a KPS > 70, and a re-irradiation dose >30.6 Gy. Twenty-two percent of patients required a treatment break due to acute toxicity. Late toxicity was primarily chronic Grade 3 diarrhea (17%) and small bowel obstruction (15%) which was significantly less for the hyperfractionated regimen.

Two additional studies have examined hyperfractionated RT in the re-irradiation setting with some success. The STORM prospective trial from Italy included 59 patients who underwent concurrent 5-FU based chemoradiation to dose of 30 Gy in 25 fractions with a boost to the gross tumor of 10.8 Gy in 9 fractions, all delivered twice a day [145]. A retrospective report from MDACC described a regimen of concurrent capecitabine-based chemoradiation with a similar biologically equivalent dose of 39 Gy in 26 fractions twice daily (less for <1 year from prior RT) with some patients receiving an IORT boost [146]. Both studies were of comparable size and reported similar 5-year local control (33–39%) and OS rates (25–39%). Surgical management and R0 resection were associated with improved local control. Further, both reports identified an increased duration from the prior treatment to recurrence as predictive of better OS. The STORM study noted very few late toxicity events and an excellent 2-year pain-free survival of 89.1%.

The studies and trials examining therapy for recurrent rectal cancer are summarized in Table 21.7. Depending upon patient selection, RT technique used, and incorporation of combined modality therapy, the 5-year local control and overall survival rates range from 35% to 70% and 25% to 55%, respectively. It is important that patients with recurrent rectal cancer are evaluated for surgical resection and negative resection margins obtained if possible as radiation therapy alone cannot replace surgery. Re-irradiation is a possibility for patients, particularly if there is a long duration (>2 years) since the prior therapy. IORT either as HDR-IORT or IOERT allows the Surgical and Radiation Oncologist to boost areas at risk for microscopic disease and has better local control with negative resection margins.

Table 21.7 Radiation therapy for recurrent rectal cancer

Study	N	Median F/U	RT	RT dose	Chemo	Outcomes	Complications
U. Kentucky (2002) [144]	103	24 mo	Hyperfx	30Gy/25 BID 30.6Gy/17 QD Boost: 6 – 20Gy	5-FU	5-year OS = 19%	Treatment break = 22% Late Gr 3 GI = 36%
STORM (2006) [145]	59	36 mo	Hyperfx	30Gy/25 BID Boost = 10.8Gy	5-FU	5-year LC = 39% 5-year OS = 39%	Acute Gr 3 GI = 5.1% Late Gr 3/4 = 1%
MDACC (2010) [146]	50	25 mo	Hyperfx	39Gy/26 BID If <1 year from RT: 30Gy/20 BID	Xeloda	5-year LC = 33% 5-year OS = 25%	3-year Late Gr 3/4 = 35% 4% Acute Toxcity

N: # Patients; *F/U* follow-up, *RT* radiation therapy, *Gy* gray, *mo* months, *LC* local control, *OS* overall survival, *Hyperfx* hyperfractionated, *BID* twice daily, *QD* daily, *Gr* grade, *GI* gastrointestinal

Long-Term Side Effects of Radiation Therapy to the Pelvis

The late toxicity secondary to post-operative radiation therapy (PORT) in rectal cancer is well established. Studies of prospective and retrospective trials both in the US and Europe revealed significantly increased long-term gastrointestinal toxicity after treatment. The Danish trial of PORT versus surgery alone demonstrated significantly worse anorectal and bowel function in 93 of their long-term survivors without recurrence [147]. A retrospective assessment of late effects after PORT in patients treated at the Mayo Clinic revealed increased frequency, clustering and urgency of bowel movements as well as more frequent fecal incontinence (39% vs 7%) requiring a pad (41% vs. 10%) [148]. Adjusting the timing of radiotherapy during rectal cancer treatment altered the long-term sequelae.

Minimizing toxicity and potentially down-staging disease at the time of surgery influenced randomized controlled trials of pre- vs post-operative radiation therapy. In the initial report of the landmark German CAO/ARO/AIO-94 trial of pre-operative vs. post-operative CRT for LARC, a statistically significant decrease in late serious GI toxicity was observed (14 vs 24%) when patients were stratified by actual treatment received [12]. The improved toxicity profile of neoadjuvant radiation is likely due to both decreased treatment volume and less extensive surgery (lower anterior resection is more common than abdominoperineal resection). Concurrent chemotherapy does add additional toxicity to RT. More serious late-term complications including a permanent stoma (73%) and bowel obstruction (28%) after pre-operative long-course (50 Gy) CRT versus RT alone for unresectable T4 disease as was found in a Norwegian study, although these differences were not significant [149]. With respect to short-course (5 × 5 Gy) vs. long-course chemoradiation (50.4 Gy with 5-FU), no differences in patient-reported late quality of life or bowel and sexual function was found in a Polish randomized trial of 316 patients [150].

Gastrointestinal toxicity is a well-known late side effect of combined modality therapy for locally advanced rectal cancer. A recent meta-analysis including 25 studies and over 6500 patients reported a 67% increased risk of fecal incontinence [151]. Serious GI complications including the risk of small bowel obstruction (SBO) were found to be higher (13.9 vs 5.5%) in the pre-operative Swedish Rectal Cancer Trial [152, 153] where SBO correlated with higher-energy X-rays (12 MV). There are acute urinary side-effects (polyuria, dysuria and urgency) associated with radiation, but there is often little increase in late urinary toxicity unless the bladder or ureters are manipulated during surgical resection or if the tumor is more advanced (T4) [154]. Sexual dysfunction after pelvic irradiation is a very frequent observation often made more complex by the age of the patient. For women receiving pelvic irradiation, the use of a vaginal dilator may decrease the risk of vaginal stenosis. However, studies investigating vaginal dilator use are fraught with patient compliance and reporting issues that may obscure any potential benefit [155]. Specific radiation dose constraints (maximum dose) to the vaginal mucosa may reduce the rates of vaginal stenosis and improve the QOL [156]. Another important consideration for older female patients receiving pelvic irradiation is treatment with Vitamin

D and calcium, particularly for those with osteoporosis. This is due to a rate of sacral insufficiency fractures of around 7% after RT for rectal cancer which can cause significant pain [157]. Finally, pelvic irradiation for rectal cancer does significantly increase the risk of secondary malignancies within the radiation treatment field (relative risk = 2.04) [158]. However, this risk is outweighed by the benefit of adjuvant radiation significantly decreasing the risk of local recurrence even if a secondary cancer is counted as a competing event.

The management of rectal cancer patients with combined modality therapy including radiation is constantly evolving, particularly with respect to advances in radiation treatment techniques. Lower rates of long-term toxicity were noted in a large Swedish systematic review when comparing more modern radiotherapy with older studies [159, 160]. In North America, the fractionation schedule for long-course chemoradiation is lower than many historical trials from which late toxicity is reported (1.8 vs 2.0 Gy) and where radiobiology predicts less late normal tissue toxicity for the same total dose (~50 Gy). Prone positioning during radiation therapy may be less of an issue with more frequent application of IMRT, but should be routinely use for post-operative RT due to the larger treatment volumes and displaced bowel.

Summary

The application of radiation to the treatment of rectal cancer is continuously evolving. As our ability to stage rectal cancer with minimally invasive procedures improves, individualized treatment plans may be possible. Currently, surgery remains the primary treatment for most stages of rectal cancer. The role of radiotherapy in rectal cancer is summarized in Table 21.8. In certain locally advanced cases, efforts are underway to pursue non-operative management and/or potentially avoid radiation altogether. For most T3 or T4 tumors and those with nodal disease, neoadjuvant chemoradiation remains central to disease management and the standard of care. Certain distal early stage tumors may also benefit from combined modality therapy to reduce the morbidity associated with standard TME by facilitating local excision. Intensity modulated radiotherapy is increasingly being used for rectal cancer as physician experience improves. It serves as a potential approach to reduce radiation-related short- and long-term side effects. The arsenal of molecularly targeted agents in cancer therapy is constantly increasing and some of these may prove synergistic with radiation treatment in rectal cancer. Hopefully the future will bring tailored therapy that maximizes oncologic outcomes while minimizing adverse effects for the majority of rectal cancer patients.

Table 21.8 Potential Role of Radiation by Stage for Rectal Cancer

Stage	Standard therapy	Radiotherapy options
cT1N0	Local excision or TAR	Endorectal brachytherapy PORT for high-risk features
cT2N0	TAR	Neoadjuvant CRT (50.4–54 Gy) ± surgery (LE or TAR) Endorectal brachytherapy PORT (50.4 Gy) ± chemo for high-risk features
cT3N0	CRT or surgery alone	Short-course RT (5 Gy × 5) PORT (50.4 Gy) ± chemo for high-risk features **NOM:** CRT ± surgery (distal tumors) Induction chemo ± CRT ± Surgery (distal tumors)
cT1-2/N1-2	CRT	**NOM:** CRT ± surgery (distal tumors) Induction chemo ± CRT ± Surgery (distal tumors)
cT3-4/N1-2	CRT	**NOM:** CRT ± surgery (distal tumors) CRT → surgery ± brachytherapy
pT3-4 or N1-2	Post-op CRT	N/A
M1	Systemic chemotherapy	Short-course RT (5 Gy × 5) → surgery CRT (50.4 Gy) → surgery SBRT (15–20 Gy × 3) to hepatic or pulmonary lesions
Recurrent	Surgery	Surgery + IORT (10–20 Gy) Hyperfractionated RT (30 Gy/25 fx BID) ± CAP/5-FU CRT (50.4 Gy) if no prior RT
M1/Palliative	Systemic chemotherapy Hospice care	Selective RT for symptomatic lesions (8 Gy × 1 / 3 Gy × 10)

c clinical stage; *p* pathologic stage; *TAR* transabdominal resection; *CRT* chemoradiotherapy; *LE* local excision; *PORT* post-operative radiation therapy; *NOM* non-operative management; *RT* radiotherapy; *SBRT* stereotactic body radiation therapy

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Part VI
Chemotherapy and Biologic Treatments

Chapter 22
Chemotherapy and Biologic Therapy in Rectal Cancer: An Update

Rob Glynne-Jones and Marcia Hall

In the metastatic setting, fluoropyrimidines, oxaliplatin and irinotecan form the chemotherapy backbones for treatment. If all are used sequentially, median overall survival ranges from 18 to 20 months. The addition of targeted agents such as vascular endothelial growth factor (VEGF) inhibitors and epidermal growth factor receptor (EGFR) inhibitors to combinations of the above with extended RAS and Braf assessments have more benefit in left-sided tumours and appear to extend median survival to 30–34 months. Meta-analyses suggest that adding biologic agents to systemic chemotherapy in patients with initially unresectable metastatic colorectal cancer improved resection rates. This strategy is beginning to be examined in rectal cancer. In the metastatic setting combinations of surgery, radiotherapy, chemotherapy, and other localized treatments such as Radiofrequency Ablation (RFA) for oligometastases are utilized and can extend survival further. Novel biological and immunological agents are being explored and the recent success of immunotherapy with anti-programmed death 1 (PD-1) checkpoint inhibitors in selected mCRC patient subgroups (patients with Microsatellite high (MSI-H) tumours) is promising. Several phase III trials are in progress.

However, the variety of genetic and epigenetic mechanisms involved in the different pathways of carcinogenesis confers considerable heterogeneity for rectal cancer. This diversity and the difficulty in defining useful and appropriate endpoints, probably reflects our inability to demonstrate robust predictive biomarkers for response. In this chapter we focus on the current systemic therapeutic options in treating locally advanced rectal cancer (LARC) and metastatic rectal cancer (mRC) and review the activity and toxicity of current cytotoxic, biological and immunological agents with and without radiotherapy. Selection of the most appropriate treatment approach remains a complex issue, with many open questions.

R. Glynne-Jones (✉) · M. Hall
Mount Vernon Cancer Centre, Northwood, Middlesex, UK
e-mail: Rob.glynnejones@nhs.net

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Introduction

One third of all colorectal cancers (CRC) arise in the rectum. Due to differences in anatomy, location, function, and molecular biology, patients with primary rectal cancer have a different natural history and require different neo-adjuvant treatment strategies and surgical approaches when compared with colon cancer. Historically, poor surgical techniques using blunt dissection, without radiotherapy (RT), gave rise to a high rate of local pelvic failure (25–30%), which used to dominate decision-making. The addition of postoperative adjuvant CRT and more recently preoperative RT/CRT significantly reduced the incidence of local recurrence [1, 2]. Preoperative treatment has been shown to be more effective in reducing the risk of local recurrence with less acute toxicity than postoperative CRT [3]. However, a significant change in surgical technique with the adoption of total mesorectal excision (TME) has reduced local recurrence rates to below 10% and supported a more selective approach to the use of RT. This issue is discussed extensively in Chap. 6. Approximately 20–30% of patients will present with metastases at the time of diagnosis [4], and subsequently up to 40% of patients will eventually develop metastatic disease [5]. Hence, in rectal cancer, the risk of metastatic disease has now almost supplanted concern for loco-regional recurrence.

Developments in imaging have permitted the selection of appropriate treatment options in patients with rectal cancer according to their relative risks of local and distant recurrence. Computerised tomography (CT) gives poor anatomical and structural definition of the rectum/mesorectum but can determine the presence/absence of metastatic disease. Imaging with MRI has a high sensitivity for assessing the depth of tumour penetration [6, 7] the presence of extramural vascular invasion (EMVI) [8] and the proximity of tumour to the mesorectal fascia or circumferential margin (CRM) [9]. The proximity of tumour to the circumferential margin in the pathological specimen is crucial to outcomes [10].

Correlation of MRI and histopathology in patients enrolled in the MERCURY trial showed that primary tumours located >1 mm from the circumferential margin have a low risk of R1 resection [11, 12]. However as MRI techniques develop, there are still variations in opinion about the whether there is or is not involvement of visible nodes where in rectal cancer the majority of involved nodes are <5 mm in diameter [13].

By contrast, patients with a low risk of local recurrence can also be identified; namely where none of the risk factors such as a threatened CRM, where the longest tumour diameter >60 mm, tumours with poorly differentiated/mucinous features, or where there is pelvic side-wall nodal enlargement are evident on pretreatment imaging. These patients have a local recurrence of only 1.4% overall [14] even without additional postoperative treatments (either postoperative adjuvant CRT or chemotherapy). Such patients with LARC may not require CRT and achieve good local control with TME alone [14]. In other patients the presence of EMVI may discriminate a group with a very high risk of both local and systemic recurrence.

The 5-year survival of rectal cancer patients has improved over recent years [15]. Different strategies utilising chemotherapy with or without chemoradiation (CRT) and short-course preoperative radiation therapy (SCPRT) have attempted to prevent both local recurrence and reduce the risk of distant metastases (Table 22.1). In a

Table 22.1 Early trials of SCPRT and CRT showing use of current indices of quality

	MRI mandated	EUS mandated	TME mandated	Good quality TME	Median no of nodes resected
Trials of SCPRT					
Swedish Rectal	No	No	No	?No	Not stated
Dutch TME	No	No	Yes	50%	7
Polish	No	No	Yes?	?	9
CR07	No	No	No	50%	11
TROG-0104	If US not possible	Yes	No	No data	Not stated
Trials of CRT					
German AIO	**No**	**Yes**	**No data**	**No data**	**Collected but not stated**
EORTC 22921	No	No	No	TME 38%	7 after CRT
FFCD 9203	No	No	No data	No data	Not stated
NSABP R03	No	?	No	No data	Not stated
Polish	No	No	?No	No data	8
TROG-0104	Some	Yes	?only later	No data	Not stated

SCPRT short course preoperative radiotherapy, *CRT* chemoradiation, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasound, *TME* total mesorectal excision

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recent population-based audit of rectal cancer using registry data from Sweden and Norway, the different treatment strategies (CRT or SCPRT) were compared. Both reduced local recurrence rates, but neither had a clear impact on survival. Despite these different radiation-based approaches and the use of TME, there was no difference in the rate of distant metastases in radically resected patients between the countries [15]. Additionally RT/CRT increased surgical morbidity, contributed to poor function and caused well-recognised long-term late-effects [16]. It is also well recognized that preoperative RT/CRT can compromise the delivery of any subsequent postoperative adjuvant chemotherapy [17].

Future biomarkers may predict response to different forms of treatment for rectal cancer. The Cancer Genome Atlas (TGCA) Network analysis has clarified genomic profiles in CRC which can differ between colon and rectal cancer [18, 19]. Consensus definitions of the CRC subtypes may now drive future research. Most colorectal cancers demonstrate activation of the wnt/β-catenin pathway, partly due to inactivation of the tumuor suppressor gene, APC, but rectal cancer has a predominant mesenchymal subtype where RAS (KRAS or NRAS) mutations are detected in over 50% of patients [20]. BRAF mutations are rare (5–10%) [21] and even rarer in rectal cancer (2%) [20]. HER-2 amplification is reported in 2–5% of colorectal cancers and represents an emerging target [22]. Patients having tumours with a common transcriptional subtype, demonstrating high Wnt signalling, stem cell and mesenchymal signatures may gain less benefit from adjuvant chemotherapy [23]. In contrast, some molecular subtypes are strongly associated with response to FOLFIRI [24].

In this chapter we examine the current systemic therapeutic options in treating locally advanced rectal cancer with pelvic radiation and induction, concurrent, consolidation and postoperative adjuvant chemotherapy. We examine how to manage rectal tumours that have not shrunk with neoadjuvant CRT. These authors agree in principle with the evidence-based recommendations to assist in the management of patients with mCRC [25]. In addition, we report recent results in metastatic rectal cancer (mRC) by reviewing the activity and toxicity of cytotoxic and biological agents, the possible schedules, and aims of treatment in adjuvant and first-line, metastatic settings. We discuss future potential strategies to reinvigorate the immune system. We also discuss therapies and novel strategies which are current active areas of research in rectal cancer.

Cytotoxic Agents Used in the Management of Rectal Cancers

Fluoropyrimidines

Since the early 1980s, the fluoropyrimidine – 5-Fluorouracil (5-FU), and more recently combinations of intravenous and oral fluoropyrimdines partnered with oxaliplatin or irinotecan, have represented the mainstay of chemotherapy treatment for patients with advanced/metastatic colorectal cancer. The short half-life of 5-FU

provides the rationale for the use of prolonged venous infusions (PVI), which allows delivery of near to maximum doses with minimal toxicity. A combination of both bolus and infusional 5-FU with folinic acid comprise the widely used 'de Gramont' regimen. Oral administration of fluoropyrimidines allows dose flexibility and can facilitate prolonged drug exposure, while avoiding the inconvenience of infusion pumps and their associated complications. The oral fluoropyrimidine prodrug capecitabine generates 5-FU within the tumour [26], and is widely used both as single-agent therapy and in combination. Tegafur is a different fluorinated pyrimidine. Significant neurotoxicity was observed when administered intravenously [27] and hence it was developed as an oral formulation, which is then metabolised to 5-FU, mostly in the liver. Tegafur–uracil, is a combination of tegafur and uracil. Uracil is metabolised by DPD and competes with 5-FU for the enzyme when they are co-administered, prolonging the half-life for 5-FU and mimicking continuous infusion [28].

Finally, S-1 is an oral fluoropyrimidine combining the 5-FU prodrug tegafur with two modulators, gimeracil and oteracil potassium. Phase III studies with S-1 in mCRC have been conducted mainly in Asian populations. S-1 has been compared with UFT in a phase III study in the adjuvant setting for curatively resected stage II/III rectal cancer in Japan [29], and appears superior in terms of disease-free survival (DFS). We are not currently aware of any studies which compare capecitabine with other oral fluoropyrimidines.

Thymidine phosphorylase (TP) is expressed more in tumour tissue and stroma than in normal tissues and is associated with increased angiogenesis and a poor prognosis [30]. TAS-102 is a further oral agent using a novel combination of the thymidine-based nucleoside analogue trifluridine (FTD) and tiparacil – a thymidine phosphorylase inhibitor [31, 32]. These initial studies, in heavily pre-treated patients with mCRC, (90% of whom were considered refractory to fluorouracil), demonstrated an improved median overall survival (OS) of around 2 months (HR 0.68) with only 17% more G3 adverse events (neutropenia) recorded in the TAS-102 treated group versus placebo. Further recent phase III evidence has provided similar results [33, 34]. Experiments on colorectal cancer cells *in vitro* suggest there may be a future role for integrating trifluridine in novel combination chemoradiotherapy regimens in patients with rectal cancer [35].

Irinotecan/FOLFIRI

Irinotecan, a topoisomerase I inhibitor, which inhibits DNA replication, transcription and repair, is active as a single agent in metastatic colorectal cancer, but has substantial toxicity. Phase III trials comparing the combinations of 5-FU/leucovorin with and without irinotecan in metastatic CRC have demonstrated superiority of the doublet regimen in terms of response rates (increased from 21–22% to 35–39%), progression-free survival (PFS) and OS [36, 37]. Response rates of FOLFIRI combined with an additional biological agent are even higher [38–40]. Despite this

efficacy in the metastatic setting, irinotecan and combinations of irinotecan have failed to show a benefit in DFS/OS in the adjuvant CRC postoperative setting [41–43].

Oxaliplatin/FOLFOX/XELOX

Oxaliplatin is a platinum analogue that forms adducts with the double-stranded DNA structure and which intercalates to prevent strand separation normally required for replication and transcription. Oxaliplatin has little activity as a single-agent in CRC and is more effective when used in combination usually with a fluoropyrimidine [44]. In an early randomised phase III study, the combination of oxaliplatin with leucovorin and infusional 5-FU (de Gramont regimens) in metastatic CRC significantly increased response (50.7% versus 22.3%, p = 0.0001), and improved PFS (median 9.0 versus 6.2 months; p = 0.0003) when compared with the de Gramont regimens alone, resulting in an acceptable toxicity with no deterioration in quality of life [45]. Hence combinations of infusional 5-FU and oxaliplatin **(FOLFOX)** and capecitabine and oxaliplatin **(XELOX)** are standard first-line therapies in mCRC.

Randomised trials have confirmed a benefit for the addition of oxaliplatin in the adjuvant setting in colon cancer [46, 47]. Patients with rectal cancer were excluded from these landmark studies because of the potential toxicity and confounding impact of radiotherapy and chemoradiation. Although the phase III trials testing the addition of new biological agents, bevacizumab and cetuximab, in CRC, confirmed the DFS/OS advantages for FOLFOX/XELOX (control arms of **AVANT, NSABP C-08, NO147**) it is still not absolutely clear if these findings can be extrapolated to those with primary rectal cancer. More recently clinical responses in the range of 35–50% have been reported with 2–3 cytotoxic drugs and up to 40–60% with the addition of biological agents. Finally, clinical responses of up to 65–89% have been observed in phase II studies with 4 drug regimens (FOLFOXIRI plus biological agents) [48, 49].

Biological Agents Used in the Management of Rectal Cancer

Five molecular targeted agents (cetuximab, panitumumab, bevacizumab, aflibercept, ramucirumab) have been assessed in conjunction with standard chemotherapy regimens for CRC, attempting to improve response rates and to extend the PFS/OS, all with varying outcomes [50–56]. Oral Regorafenib as a single-agent is also used in second-line or salvage therapy. Although the implementation of the agents into standard of care is a matter of ongoing debate, to a greater or lesser degree they contribute to prolonging survival of patients with mCRC. In some selected cases, biological agents can help convert unresectable (usually liver) metastases to resectable lesions and occasionally result in cure. Many other biologically-targeted therapies have been examined in phase I/II trials but have not shown sufficient activity to proceed further.

Cetuximab, Panitumumab and the EGFR Pathway

The epidermal growth factor receptor (EGFR) is a 170-kD trans-membrane glycoprotein. It is one of 4 members of the Erb-B family of proteins and is also known as the Erb-B1 or HER-1 receptor, the remaining three being Erb-B2 (HER-2), HER-3 and HER-4. These receptors are part of complex and inter-related downstream signalling pathways including the *ras-raf* mitogen activated protein kinase (MAPK) pathway which controls cell-cycle progression and proliferation and which has roles in DNA repair [57–59]. EGFR is over-expressed in 60–80% of colorectal cancers and this is associated with a more aggressive phenotype and poor response to conventional therapy via acquired resistance to both chemotherapy and radiotherapy [60, 61]. The EGFR pathway can be targeted either through monoclonal antibodies (e.g. cetuximab, panitumumab), small molecule tyrosine kinase inhibitors (TKIs e.g. regorafenib), anti-sense nucleotides, ligand toxins or inhibitors of the downstream effectors of the EGFR signalling pathway (Akt, MAPk etc.).

Cetuximab is a chimaeric monoclonal antibody directed against the extracellular domain of the EGFR. The side-effects of an acneiform rash and diarrhoea can be troublesome and frequently require additional supportive medication. **Panitumumab** is a fully humanised IgG2 monoclonal antibody against human EGFR. Currently in CRC, the monoclonal antibodies cetuximab and panitumumab have activity as single agents and increased response rates are achieved when these are added to standard chemotherapy schedules [52, 62–65]. These approaches have led to corresponding increases in both PFS and OS. Colorectal cancer patients with tumours bearing mutations of *KRAS,* downstream of the EGFR signal, do not, however, respond to EGFR monoclonal antibodies [66]. *KRAS* exon 2, 3 or 4, *NRAS* exon 2 or 3 and *BRAF* mutations all predict resistance to EGFR treatment [55, 65, 67–70]. Recently it has been demonstrated that right-sided tumours even if wild type Ras do not benefit from these agents to the same extent as left-sided tumours [40, 71–73]. Hence, updated National Comprehensive Cancer Network guidelines (version 2. 2017) (www.nccn.org/professionals/physician_gls/f_guidelines.asp) recommend EGFR antibodies should be combined with first-line treatment in only mCRC patients with RAS wild-type and left-sided tumours. Discordance in *K-RAS* status between the primary tumour and metastatic sites compounds treatment decisions and could be more common in rectal patients with lung metastases [74].

Bevacizumab/Aflibercept/Ramucirumab and Antiangiogenesis

Anti-angiogenic agents modify and normalise the existing vasculature, inhibiting new blood vessel formation and improving the delivery of cytotoxic drugs. Pre-clinical and clinical studies suggest that VEGF-A is the predominant angiogenic factor in this development. VEGF has direct effects on endothelial cell function including activating survival proliferation and migration pathways.

VEGF may also inhibit dendritic cell maturation and enhance the adhesion of natural killer cells to tumour microvessels. Tumour growth, tumour invasion and the development of distant metastases appear dependent upon this process of angiogenesis [75].

Bevacizumab is a recombinant humanized monoclonal antibody which binds to the VEGFR ligand and prevents VEGF-A from interacting with its target receptor. Bevacizumab has shown modest benefits in terms of OS [76] for patients with metastatic colorectal cancer [50, 77], but randomised studies have not proven the advantage of anti-VEGF therapy in the adjuvant setting [78, 79]. However several studies have reported survival differences between patients with rectal and colon cancer treated with bevacizumab-containing regimens, rectal cancer patients having a longer PFS ranging from 4.5 to 8 months [80–82]. These findings actually generate several hypotheses and require validation with data relating to precise primary tumour location.

Aflibercept is a VEGF-trap with a different molecular structure and mechanism of action. It is a fully humanized recombinant fusion protein that binds VEGF-A, VEGF-B and placental growth factor (PGF)-1 and 2 with higher affinity than bevacizumab. In a placebo-controlled trial of aflibercept/placebo with FOLFIRI, the addition of aflibercept demonstrated efficacy in second-line treatment of patients with metastatic CRC, where it improved median PFS by 2–3 months (6.90 vs 4.67 months, HR, 0.758 $P < .0001$) and provided a modest gain in OS (13.5 vs 12.0 months, HR: 0.82, $P = 0.0032$) [83]. This survival benefit with the addition of aflibercept was noted in patients who were bevacizumab naïve as well as those who were previously treated with bevacizumab [84]. But there was no difference in PFS at 12 months for metastatic colorectal cancer patients treated first-line in an open-label study of mFOLFOX6 +/− aflibercept [85].

Ramucirumab is a fully human IgG1 monoclonal antibody against the vascular endothelial growth factor receptor VEGFR-2. In a phase III study of metastatic CRC patients (who had failed first-line treatment with bevacizumab, oxaliplatin and 5fluorouracil), ramucirumab combined with FOLFIRI improved OS (13.3 versus 11.1 months, HR- 0.84, p = 0.0219) [86]. All patients had previously received bevacizumab and the benefit was similar for patients with *KRAS*-mutated and wild-type tumours. Ramucirumab also modestly extended median PFS from 4.5 months to 5.7 months (HR 0.79; 95% CI [0.70, 0.90]; p = 0.0005).

Overall, the differences in PFS and OS between treatment arms are modest for drugs that target the VEGF pathway in the first-line setting. When considered in the context of more significant effects of other combinations such as 5-FU/FA [87], and the IFL regimen [50] or in second-line therapy [77, 83], the addition of a biological agent appears limited in combination with relatively effective chemotherapy backbones. No predictive biomarkers for the benefit of VEGF inhibitors with any chemotherapy backbone have yet been established [88]. Consequently, optimal utilization of the available anti-angiogenesis options remains an unfulfilled goal.

Regorafenib and Multi-tyrosine Kinase Inhibitors (TKI)

Regorafenib is an oral TKI targeting both angiogenic and stromal tyrosine kinases, including human VEGFR2, tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (TIE-2), fibroblast growth factor receptor 1, platelet-derived growth factor receptor and oncogenic kinases such as KIT, RET and BRAF. Activity is modest with a median reported difference in OS of 1.4 months [89]. However, all patients in this study had previously received bevacizumab and EGFR antibodies (for *K-RAS* wild-type cancers). Regorafenib could have more anti-tumour activity in less pre-treated patients [90] however, a common adverse side-effect profile with profound fatigue, palmar plantar syndrome, loss of appetite, diarrhea and a sore mouth limits its use.

Other Potential Novel Options

A large study of 1443 patients with CRC found that there is a gradual shift in somatic molecular characteristics along the length of the bowel, particularly in relationship to the frequency of BRAF mutations, microsatellite instability–high status and CpG island methylator phenotype (CIMP)-high tumors [91]. The TCGA analysis found no difference between colon and rectal carcinomas in copy number, CIMP, messenger RNA, and microRNA in non-hypermutated tumors [92]. Determining mutational status of any cancer can be compromised by tumour heterogeneity but in rectal cancer specifically, a low percentage of tumor DNA is common and can create low- cellularity specimens for molecular analysis [93]. Additionally, the frequent use of neoadjuvant therapies in rectal cancer has been reported to alter KRAS mutation status [94].

HER2-4 *Over Expression*

HER2 amplification or over-expression is rare in CRC but is found more commonly in distal (left-sided) tumours with an incidence of 15–25% in rectal cancers [95]. This latter study by Yao and colleagues, however, reported receptor status following preoperative RT. Two small studies have explored HER-2-targeted therapy in CRC patients whose tumours overexpressed HER2. In the HERACLES study, 27 patients with HER-2 overexpressing CRC received a combination of trastuzumab and lapatanib (anti HER1/EGFR and HER2). All patients in HERACLES had KRAS wild-type exon 2 and 3 mutations and had failed treatment with standard EGFR inhibitors (cetuximab or panitumumab). Results showed a 30% response rate to anti HER1-2 therapy and 44% achieved stable disease [96]. HER2 overexpression has been

reported at very low levels in patients with both colorectal *RAS* wild-type and mutant cancers [97]. Two further studies are investigating the role of anti-HER1, 2 and 4 combinations in HER-overexpressing, *RAS* wild-type but cetuximab-resistant colorectal cancers (NCI-NSABP FC7: neratinib with axitinib) and NCi-MATCH (trastuzumab with afatinib). Trastuzumab-DM1, the antibody-drug conjugate is also being explored in HER2-overexpressing CRC patients.

PIK3CA *Mutations/Overexpression and PI3K/AKT/mTOR Pathway*

Cancers with *PIK3CA* mutations are less prevalant in the rectum than in the right-sided colon. Tumours harbouring these mutations are often associated with KRAS mutation and those with a high degree of CpG island methylator phenotype. *PIK3CA* signalling is thought to enhance PTGS 1 and 2 (cyclo-oxygenase 1 and 2), explaining the mechanism for treatment with aspirin (post-diagnosis). Aspirin inhibits PTGS2 and prostaglandin E2, and is associated with longer survival in patients with *PIK3CA*-mutated CRC specifically [98].

BRAF *Mutations*

For patients with CRC expressing BRAF V600E mutations, a more aggressive natural history to the disease has been reported and conventional chemotherapy treatment has limited effectiveness. In this setting, BRAF inhibition (e.g. Vemurafenib) has limited value [99] and for this reason there are trials (B-CON, CRC) testing an MEK inhibitor Binimetinib with Encorafenib and Cetuximab – as triple therapy compared with the standard treatment i.e. Irinotecan/Cetuximab or Folfiri/Cetuximb in BRAF V600E-positive metastatic CRC (NCT02928224).

CpG Island Methylator Phenotype (CIMP)

Epigenetic changes in tumour DNA have been shown to alter response to therapy. Broadly, an increase in methylation of tumour DNA tends to reduce sensitivity to radiation. A distinct molecular subtype of CRC characterized by high degrees of methylation phenotypically has been described, termed CpG island methylator phenotype (CIMP) [100–102]. This occurs in about 15% of sporadic cases of CRC but only 8% of rectal cancers [103] and might be targeted by temozolamide as in gliomas. Some suggest that 06-methylguanine-DNA-methyltransferase (MGMT) promoter hypermethylation as a biomarker is poorly predictive [104] and often discordant with the original archival tissue, suggesting that fresh biopsy or plasma is needed for refining the target selection [105]. MEK inhibitors in pre-clinical data

reactivate MAPK and PI3K pathway signalling through crosstalk with HER family membrane receptors, c-MET and insulin-like growth-factor-receptor 1. Clinical trials are therefore examining MEK inhibitors in combination with different membrane receptor inhibitors.

PARP Inhibitors

A small phase Ib study [106] supports the further development of a PARP inhibitor plus CRT phase II/III trial in rectal cancer patients. However, the choice of companion PARP inhibitor, (veliparib in the Czito study), may require re-evaluation. PARP inhibitors have other modes of action in addition to preventing homologous recombination DNA repair after radiation/cytotoxic therapy- e.g. by trapping PARP at sites of DNA damage. In this respect, Homologous Repair Deficiency is not considered a major factor in rectal cancers and the low HRD scoring and lack of MSI suggests that if veliparib is active in this study, it is somehow enhancing the response to cytotoxics/radiation rather than acting solely as a PARP inhibitor. Future exploration of alternative PARP inhibitor combinations with chemoradiation may be more toxic, due to greater PARP trapping and 'off-target' effects, but this may result in improved outcomes for this population.

Mismatch Repair and Lynch Syndrome

Colorectal cancers with deficient mismatch repair (MMR-D) have high genomic instability, a high mutational burden and the potential for the expression of numerous neoantigens. Interest in patients with MMR-D CRC has been stimulated by the results of the Phase II study of pembrolizumab in metastatic CRC where Objective Response Rate (ORR) and Disease Control Rate (DCR = CR + PR + SD) were 50% and 89% for MMR-deficient CRC and 0 and 16% for MMR-proficient CRC, respectively. The median PFS was not reached for MMR-deficient CRC and was 2.4 months for MMR-proficient CRC (HR = 0.135; 95% CI, 0.043 to 0.191; P = 0.0001). The median OS was not reached in the MMR-deficient CRC cohort, as opposed to 6 months in the MMR-proficient CRC cohort (HR = 0.247; 95% CI, 0.117 to 0.589; P = 0.001). These results suggest that MMR-deficient CRC tumors receive durable benefit from anti-PD-1 therapy [107].

Immunotherapy and Checkpoint Inhibitors

Historical data has shown that patients with operable CRC have an impairment of cellular immune function [108–110] which is related to tumour burden and which independently influences prognosis. Tumours also evade the host immune defences

either by ineffective antigen presentation or mechanisms which subvert an effector response [111]. It has long been recognised that a prominent lymphocytic infiltration in the primary tumour is associated with improved survival in rectal cancer treated by surgery alone [112]. By contrast, larger progressive solid tumours usually show few tumor infiltrating T lymphocytes (TILs). More sophisticated techniques show T lymphocytes (CD3+) with cytotoxic (CD8+) and memory (CD45RO+) phenotypes within the tumour and at the invasive edge which can predict the risk of recurrence and survival and even the response to CRT [113]. Similar to the findings of Jass, the density of CD8 infiltrates is inversely correlated with the T stage [114]. Hence, the prognostic value of these T cell infiltrates trumps the conventional staging and histological prognostic factors [115].

The variability of findings in reported studies may depend upon differences in the type of cancer examined, the density and the location of immune cells evaluated (central tumour versus the invasive tumour edge) and whether or not the patient has received chemotherapy and/or preoperative RT. Specifically, Oxaliplatin and bevacizumab may have minor immune effects. In this regard, in pre-clinical mouse models Oxaliplatin can activate the immune system against colorectal cancer cells [116]. Vascular endothelial growth factor VEGF-A also limits T cell recruitment, promotes T-Cell exhaustion and induces proliferation of immunosuppressive cells (Regulatory T cells – Tregs and Myeloid-derived suppressor cells – MDSCs) [117]. In the clinical setting, in the presence of macroscopic tumour, FOLFOX/FOLFOXIRI and bevacizumab may decrease granulocytic MDSCs and increase pro-inflammatory helper T-cell (Th17) frequency, thereby producing a micro-environment favorable to immune checkpoint inhibitor treatment [118].

The anti-PD1 checkpoint inhibitors have been investigated in patients with mCRC with coincident mismatch repair deficiency. In a trial of pembrolizumab enrolling MSI-H colorectal cancers [119], MSI-H non-colorectal cancers, and MSS colorectal cancers 16/25 (57%) of patients achieved objective responses and an additional 9/25 (32%) had stable disease many of whom have sustained the duration of this disease control. The median OS was not reached in the MMR-deficient CRC cohort, as opposed to 6 months in the MMR-proficient CRC cohort (HR = 0.247; 95% CI, 0.117 to 0.589; P = 0.001) [120]. In a different trial using nivolumab in MSI-H tumors, 12/47 evaluable patients (26%) achieved an objective response and an additional 14 patients (30%) achieved stable disease [121]. This has led to an approval in NCCN guidelines for the use of Pembrolizumab or Nivolumab (anti-PD-1 antibodies) for the treatment of metastatic CRC in patients with defects in mismatch repair. The results of these preliminary trials have sparked enthusiasm for testing immunotherapy in hypermutated colorectal cancers. In this respect, KEYNOTE 164 Phase II (NCT02460198) administers Pembrolizumab as a single-agent only to 60 patients with previously treated metastatic mismatch repair related colorectal cancer (MSI-Hi or MMR deficient). The KEYNOTE 177 (NCT02563002) is an international, randomized, open-label, phase III study of pembrolizumab versus standard-of-care chemotherapy in first-line MMR-deficient or MSI-high metastatic CRC aiming to recruit 270 patients. Interestingly, eligible patients can continue pembrolizumab beyond progression. Patients in the standard of care arm who have

progressive disease (PD) and meet crossover criteria may be eligible to receive pembrolizumab for up to 17 treatment cycles [122].

Cobemetinib, a MEK inhibitor has been tested in combination with atezolizumab (an anti-PD-L1 antibody) in *KRAS* mutant mCRC and 3 of 23 with MMR-proficient tumours (and 1 where MMR status is unknown) achieved PR, where 5 further patients had stable disease [123]. A phase III study is currently underway. Epigenetic priming using histone deacetylases and/or DNA methyltransferases can induce immune susceptibility *in vivo* and this approach is being evaluated in an ongoing pilot study in MMR-proficient advanced CRC (NCT02512172). However, patients with MMR-D or MSI-H CRC represent only a tiny subset of the metastatic population [124] and those with primary rectal cancer only about 2–4% overall [20, 125, 126]. Both Lynch syndrome and sporadic mismatch repair-associated tumours are very rare in patients with rectal cancer [127] hence, at present immunotherapy has little proven relevance in metastatic rectal cancer patients. Combinations with radiotherapy are being explored in locally advanced rectal cancer using Dervalumab and Tremelimumab (NCT02888743) Nivolumab (NCT02948348) and Pembrolizumab with CRT (NCT02586610).

Chemoradiation for Rectal Cancer

Trials in the 1980s established that treatment of Dukes B and C rectal cancers after curative surgery with either radiotherapy [128] or chemotherapy alone or combined chemoradiation which increased the DFS and reduced local recurrence when compared with surgery alone [129, 130]. Combined chemoradiation was the most effective therapy and improved OS. Subsequent postoperative rectal cancer trials examined the difference between radiation alone or chemotherapy alone and chemoradiation [131, 132]. The NCCTG 79-47-51 study treated patients with a higher dose of radiation alone or sandwiched between 4 cycles of 5-FU based chemotherapy [133]. Marked reduction in recurrences in the chemoradiation arm (42% versus 63%) prompted the National Institute of Health to recommend chemoradiation after surgery for rectal cancer as standard treatment [134]. However despite postoperative radiation/chemoradiation, local recurrence rates were still reported in 13–25% patients.

In a landmark German CAO/ARO/AIO – 94 trial [3] 823 patients with cT3-4 or node positive cancers were randomised between pre-and post- operative CRT using PVI-5-FU during the first and fifth weeks of radiation. All patients were scheduled to receive post-operative adjuvant chemotherapy. Loco-regional failure was only 6% in the preoperative arm versus 13% in the post-operative arm. There was no difference observed in the incidence of distant metastases, DFS or OS. The 10-year follow-up showed 17 of the 38 local recurrences in the postoperative arm observed in the 145 patients who did not receive CRT [5]. The superiority of preoperative over postoperative chemoradiation in terms of DFS was confirmed in the NSABP R03 trial [135]. Neoadjuvant CRT has led to effective tumour down-staging/

down-sizing and 15–25% of the patients show a pathological complete response (pCR) – defined as no residual cancer found on histological examination of the TME specimen [136].

Selective postoperative chemoradiation on the basis of a pathologically involved CRM has been shown to be inferior to blanket SCPRT [137]. Thus the current standard of care for locally advanced rectal cancer is neoadjuvant SCPRT [1, 138] or chemoradiation followed by surgery including total mesorectal excision [3, 134]. The local recurrence rate following this practice is <10% [3, 139].

The Chemotherapy Component to CRT

Fluoropyrimidines remain the mainstay of concurrent chemoradiation regimens in rectal cancer. In randomized phase III trials, the addition of 5-FU to preoperative radiation tripled the pathological complete response rate (pCR) from 4–7% to 12–17% and halved the local recurrence rate, with a manageable increase in acute toxicity [17, 140]. Subsequent small studies of concurrent CRT using capecitabine [141, 142] or bolus 5-fluorouracil/leucovorin and capecitabine [143] and tegafur-uracil (UFT) [144] have also been undertaken. All appear to show equivalent toxicity and efficacy. The topic has been recently extensively reviewed [145]. Larger randomised studies have confirmed the equivalence in terms of toxicity and outcomes of PVI 5-FU versus capecitabine in chemoradiation schedules [146, 147].

The addition of a modest dose of 5-FU to preoperative radiation increases the pCR rate over radiotherapy alone [17] and improves loco-regional control [17, 140, 148]. Prolonged venous infusions of 5-fluorouracil or oral capecitabine during CRT are recommended rather than bolus 5-FU [146, 147]. The NSABP R04 study demonstrated that intravenous 5-fluoruracil (5-FU) or the equivalent prodrug capecitabine have equivalent effects [149]. Current standard practice is to use capecitabine 800–900 mg/m^2 twice daily for 5 days each week (Monday–Friday) of the 5 weeks radiation therapy. Adding oxaliplatin to 5-FU in the adjuvant treatment of patients with CRC improves disease-free and overall survival [46, 47, 150]. Encouraging phase II data supported the addition of oxaliplatin into preoperative CRT regimens [137, 151, 152] where it was anticipated that such integration would further improve outcomes. However, phase III trials [149, 153] were generally disappointing and showed only an increase in the incidence of grade 3/4 diarrhoea. Although meta-analyses indicate that concurrent oxaliplatin added to CRT may slightly increase pCR rates and DFS in selected patients, the enhanced acute toxicity may have a negative impact on compliance [154] and the use of oxaliplatin as a radiosensitizer is not currently recommended.

The only trial suggesting benefit for the addition of oxaliplatin was the German CAO/ARO/AIO-04 trial which randomized 1265 patients between preoperative CRT 50.4 Gy coupled with bolus 5-FU alone [155] comparing the best regimen from the group's previous trial [5] versus the combination of oxaliplatin and

infusional 5-FU. Patients participating in this study also received postoperative adjuvant chemotherapy after surgery with or without oxaliplatin. Three-year DFS, the primary end-point, was significantly improved from 71% to 76% (HR 0.79, P = 0.03). Overall survival was not improved, however, and there were no differences in loco-regional recurrence (3% versus 6%), but there was a 3.9% reduction in distant recurrence recorded. The small benefit in DFS may derive from the preoperative concurrent oxaliplatin/5-FU chemoradiation component or from the postoperative oxaliplatin, or both. There is no benefit, however, with this approach in OS.

Unlike oxaliplatin, irinotecan (despite an acknowledged efficacy in the metastatic setting), failed to show advantages in DFS or OS in the adjuvant postoperative setting in colon cancer [78, 79, 156, 157]. Many small prospective phase I/II trials have shown that the addition of irinotecan to fluoropyrimidines and RT in rectal cancer is feasible with an overall increase in the rate of pCR (range 14–37% in patients receiving 5-FU/irinotecan and RT) [158–160]. Additionally, recently published efficacy results for a study comparing 5-FU and RT with either oxaliplatin or irinotecan [161] describe improved DFS/OS rates for the irinotecan- rather than the oxaliplatin-containing therapy (DFS: 68 vs 62%, OS: 85 vs 75%). The irinotecan patients also had less locoregional failure, distant failure and second primary failures (16 vs 18%, 181 vs 30% and 2 vs 6%) than those receiving oxaliplatin combinations [162]. Clearer outcomes of the efficacy and tolerability of adding irinotecan to capecitabine based CRT will emerge from the currently recruiting ARISTOTLE trial (**A**dvanced **R**ectal study w**I**th **S**tandard **T**herapy **O**r a novel agent, **T**otal mesorectal excision (TME) and **L**ong term **E**valuation) (http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=7890).

Targeted Agents and CRT

Antiangiogenics

An early Phase I/II trial in rectal cancer patients receiving bevacizumab and CRT, provided direct evidence of the decrease of tumour vascular density, tumour perfusion, tumour interstitial fluid pressure and the number of viable circulating endothelial and progenitor cells, resulting in a significant increase in apoptosis in patients receiving anti-VEGF treatment [163]. Although subsequent studies confirmed a high incidence of pCR to CRT with additional bevacizumab as a radiosensitizer, there were unacceptable perioperative complications in up to 60% of cases [164–167]. The AVACROSS study assessed the addition of bevacizumab added to induction CT with Xelox followed by preoperative CRT with bevacizumab [168]. This study showed a pCR rate of 36% with acceptable acute toxicity, but 24% of patients had surgical complications that required additional surgical intervention. Systematic reviews suggest that the pooled pCR rate is no better than that reported with 5-FU-based CRT alone and that the extra toxicity is not counterbalanced by

improvements in DFS/OS [169]. An oral antiangiogenic agent, cediranib, a potent small molecule inhibitor that inhibits several tyrosine kinases including VEGFR-1-3 and c-kit, was given concurrently with CRT to 18 LARC patients at three different dose levels. All patients completed treatment and the additional cediranib was well tolerated. An improved response to chemoradiation plus cediranib was observed with 30% having an excellent clinical or pCR versus <15% in historical series for chemoradiation alone [170].

EGFR Inhibitors/TKIs

EGFR is overexpressed in 50–70% of primary rectal cancers and its expression is related to poorer pCR rates, DFS and OS. Overexpression of EGFR in pre-clinical models also leads to radiation resistance. Cetuximab/panitumumab mechanisms of action are described above. In addition to their use with concomitant chemotherapy in *KRAS* wild-type tumours, cetuximab can safely be administered with conventional or hyperfractionated RT in patients with head and neck cancers and this has demonstrated improved survival [171, 172]. Unfortunately, numerous small trials of cetuximab/panitumumab with CRT or as part of induction chemotherapy prior to CRT for LARC, have failed to improve outcomes and have demonstrated worse quality of life and greater toxicities. Interestingly, although some studies have shown a slight increase in the incidence of pCR, these cases cannot be correlated to the *KRAS* tumour status [173]. The incorporation of cetuximab into chemoradiation was reported to offer better outcomes in *KRAS* wild-type or higher EGFR gene copy tumours [174] but this has not been confirmed in subsequent trials [175–179]. Post hoc analysis suggests that tumours maintaining wild-type p53 may be associated with increased response to cetuximab [180, 181]. In the SAKK trial the addition of panitumumab to capecitabine CRT in 40 patients with KRAS wild-type LARC, achieved a 43% rate of complete and near-complete regression (Dworak TRG2 and TRG3) [182]. Amongst the oral TKIs, when gefitinib was given with CRT for rectal cancer, the limitation was significant toxicity [183, 184]. The integration of biological agents into chemoradiation schedules is not currently supported because of increased toxicity despite a modest projected benefit.

Postoperative Adjuvant Chemotherapy in Rectal Cancer

In colon cancer, adjuvant chemotherapy has an established role for patients with ‘high-risk’ stage II and stage III disease – cutting the risk of death by approximately 20–30% with fluoropyrimidine monotherapy [185] and providing additional reductions when combined with oxaliplatin [46, 47]. Patients with rectal cancer were specifically excluded from the landmark colon cancer studies because of the confounding

impact of radiotherapy and chemoradiation. But where they were included, the improvements in reducing mortality and disease recurrence are not seen for rectal cancer patients [186]. To date 5-FU/oxaliplatin-based adjuvant therapy has been validated only in colon cancer. A recent meta-analysis found no benefit in overall survival from the addition of oxaliplatin to fluoropyrimidines in rectal cancer despite higher pathological complete response rates and modest improvements in disease-free survival [187].

More aggressive treatments remain unproven in their ability to improve outcomes, although in France FOLFIRINOX evaluation is ongoing for stage III T4 and/or N2 **(IROCAS trial;** *NCT02967289*). A Cochrane meta-analysis showed a significant benefit in DFS (HR = 0.75) and OS (HR = 0.83) for patients who received postoperative fluoropyrimidine-based chemotherapy when compared with observation alone [188]. Several trials in this meta-analysis emanate from Japan (where preoperative CRT is not routinely used and where a lateral pelvic lymph node dissection (LPLND) is commonly performed for cancers extending below the peritoneal reflection). Only one trial in this meta-analysis used preoperative CRT. By contrast, individual randomized phase III trials examining postoperative adjuvant chemotherapy following SCPRT or chemoradiation with an observation control [148, 189–191], all failed to show a significant OS benefit for postoperative chemotherapy over observation alone (Table 22.2). Reviews and meta-analyses of randomized trials [188, 191–193] have been only partly helpful in this respect.

A meta-analysis in colon cancer suggests earlier administration of adjuvant chemotherapy following surgery, is more effective [194]. In rectal cancer, the optimal time to start adjuvant chemotherapy following CRT can be as short as 5–6 weeks [195]. Compliance is poor in the adjuvant setting after CRT in rectal cancer [34] and delivery is often compromised by surgical morbidity and healing problems [196]. Patients for whom adjuvant chemotherapy was delayed ≥8 weeks after surgery had inferior local and distant recurrence rates and worse overall survival when compared with those who received chemotherapy within 8 weeks of surgery [196]. However, many oncologists continue to use a FOLFOX regimen for postoperative chemotherapy in rectal cancer, effectively extrapolating from the results with colon cancer. The National Comprehensive Cancer Network (NCCN) colorectal cancer (CRC) Guidelines recommend postoperative chemotherapy for all histopathological stages following preoperative CRT [197]. Data from a phase II trial of FOLFOX is used to support this view [198]. The trial showed an improvement in DFS for the FOLFOX arm, although the "control" arm of this trial appears an outlier as DFS is considerably lower than other reported studies [198]. After numerous randomised trials and meta-analyses, the actual role and benefit of adjuvant chemotherapy following preoperative SCPRT chemoradiation remains uncertain. Many reasons have been presented to explain this paradox [199] such as the inclusion of very low risk cases, variations in the measurement of quality of TME procedures and suboptimal CT scheduling or prolonged intervals before commencing CT in some series.

Table 22.2 Trials of postoperative adjuvant chemotherapy with randomisation following chemoradiation/SCPRT and surgery i.e. with pathological entry criteria: outcomes and hazard ratios

Trial	Patient number	Randomisation	Eligibility	Compliance	Primary end point	OS	DFS	DFS HR (P value)
QUASAR	3239 overall 948 rectal with 203 (6%) preop RT	5FU/LV regimens versus control	Uncertain indication for chemo 91% stage II	58% full chemotherapy (evaluated patients)	All-cause mortality	78% versus 73% (rectal cancer patients)	Not stated	0.78 (P = 0·001) 0.68 (P = 0·004) in rectal cancer patients
PROCTOR SCRIPT	437 Preop RT (86%) and CRT (14%)	5FU/LV regimens or capecitabine versus control	(y)p stage II/III and R0/ R1 (SCRIPT)	74% completed all chemo cycles	Overall Survival (OS)	5-year OS 80% vs 79% in control group	5-year DFS 63% vs 55% control	0.80 (P = 0·13)
CHRONICLE	113	6 cycles of XELOX (18 weeks) versus control	Preop CRT only pT0-T4yp N0-N3 R0 (>1 mm)	48% received full 6 cycles 39% dose reduced and 39% delay	3 year DFS	3 year OS 89% versus 88%	3 year DFS 78% vs 71%	0.80 (P = 0.75)
ADORE	321	4 cycles of bolus FU/LV versus 8 cycles FOLFOX (16 weeks)	ypT3–4 N0 or $ypT_{any}N1–2$ R0	95% 5FU/LV 97% FOLFOX completed all plannedcycles	3 year DFS	3-year OS 95% FOLFOX vs 86% FU/LV	3-year DFS 63% FU/LV vs 72% FOLFOX	0.66 (P = 0.047)
ECOG E3201 study (closed)	179 in 2 groups 83 (preop CRT) 96 (postop CRT)	FU/LV vs FOLFOX6 vs FOLFIRI 16 wks	Stage II/III ypT3N0M0, T4N0M0, ypTanyN1–3	No data provided	3 year OS	5 year OS 83% in both groups	5 year DFS 69%	Not stated

GERCOR	357 (69% received preop RT)	5FU/LV versus 5FU/LV + Irinotecan (IFL)	stage II (T3/T4, N0, M0) or III (any T, N1/N2, M0) R0	At least 75% of planned dose – 72% in the IFL arm versus 95% in the 5FU/LV arm	DFS	OS HR =0.87	5 year DFS 63% versus 58%	0.80 (P = 0.154)

References/Registrations:

Quasar Collaborative Group; Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study Lancet 2007 Dec 15;370(9604):2020–9

PROCTOR SCRIPT: Breugom AJ, van Gijn W, Muller EW, Berglund Å, van den Broek CB, Fokstuen T, Gelderblom H, Kapiteijn E, Leer JW, Marijnen CA, Martijn H, Meershoek-Klein Kranenbarg E, Nagtegaal ID, Påhlman L, Punt CJ, Putter H, Roodvoets AG, Rutten HJ, Steup WH, Glimelius B, van de Velde CJ; Cooperative Investigators of Dutch Colorectal Cancer Group and Nordic Gastrointestinal Tumour Adjuvant Therapy Group. 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. 2015;26(4):696–701

CHRONICLE TRIAL: Glynne-Jones R et al. Ann Oncol. 2014; 25:1356–62

ADORE TRIAL: Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, Park JO, Kim SY, Kim TY, Kim JH, Ahn JB, Lim SB, Yu CS, Kim JC, Yun SH, Kim JH, Park JH, Park HC, Jung KH, Kim TW. 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. 2014;15(11):1245–53

ECOG E3201: Benson AB, Catalan P, Meropol NJ, Giantonio BJ, Sigurdson ER, Martenson JA, Whitehead RP, Sinicrope F, Mayer RJ, O'Dwyer PJ. ECOG E3201: intergroup randomized phase III study of postoperative irinotecan, 5-fluorouracil (FU), leucovorin (LV) (FOLFIRI) vs oxaliplatin, FU/LV (FOLFOX) vs FU/LV for patients (pts) with stage II/III rectal cancer receiving either pre or postoperative radiation (RT)/FU. J Clin Oncol 2006;181:3526 (A)

GERCOR: Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229–37

Targeted Agents in the Postoperative Adjuvant Setting

Clinical trials have investigated whether this benefit from the addition of targeted agents to chemotherapy in mCRC would translate into the adjuvant setting where bevacizumab initially improved DFS in colon cancer, but where this effect was reversed after bevacizumab discontinuation [79, 156, 200, 201]. The use of cetuximab in the adjuvant setting, combined with 5-FU and oxaliplatin in CRC, has shown no advantage in DFS and indeed there is worse reported toxicity and a poorer outcome in some patients over 70 years of age [202]. There have been no adjuvant studies investigating the addition of panitumumab. The ECOG E5204 study randomised patients with clinically staged II or III rectal cancer after neoadjuvant chemoradiation followed by resection to postoperative FOLFOX for 12 cycles with or without bevacizumab (NCT00303628).

The Optimal Sequence of Postoperative Chemotherapy and Radiation

A small Korean randomised trial evaluated the optimum sequence of RT and chemotherapy in the postoperative setting. A total of 308 patients were randomized to early RT (45 Gy in 25 fractions) – starting on Day 1 of the first cycle- or late postoperative RT (starting on Day 1 of the third chemotherapy cycle). After 10 years of follow-up, there was a trend but no statistically significant advantage in DFS (71% vs. 63%; $p = 0.162$) for the administration of early RT [203].

Neoadjuvant Chemotherapy

Systemic chemotherapy treatment administered before and not after radical surgery is associated with better compliance and more favourable toxicity profiles [204]. For this reason the total neoadjuvant approach (TNT) with FOLFOX or XELOX chemotherapy prior to or subsequent to CRT in the United States has become a popular strategy and is recommended in NCCN guidelines [197] with the aim of ensuring that patients receive sufficient therapeutic doses with an appropriate intensity, which is not compromised in the event of any surgical morbidity or slow recovery.

Prior to CRT/SCPRT: Induction Chemotherapy

Induction chemotherapy, before CRT, has been shown to be feasible and can be delivered without compromising either the radiation or subsequent surgery. But it is unclear how much this strategy has added to improving outcomes. It does not appear

to increase pCR, R0 resection or negative CRM rates and may add significant morbidity [205]. Strategically, it defies the principals of De Ruysscher who advocates that the interval from the start of any treatment to the end of radiotherapy should be as short as possible [206].

Post SCPRT/CRT and Pre-operatively: 'Consolidation' Chemotherapy

Additional courses of FOLFOX after chemoradiation and before TME have the potential to increase pCR and hence theoretically could broaden the options for patients in terms of less invasive treatment strategies [207]. Sequential additional courses of FOLFOX after chemoradiation increased the pCR rate from 18% with CRT alone when surgery was performed 8 weeks later to a pCR rate of 38% when 6 courses of FOLFOX were administered and surgery was delayed to 19 weeks. An ongoing randomised phase II trial is exploring the strategy of induction versus consolidation chemotherapy when CRT is administered (NCT02008656). This strategy may assist responding tumours, but radiological response rates to further oxaliplatin-based chemotherapy after failure to respond to CRT appeared to be only 17.8% in a small retrospective study [208]. Additionally consolidation chemotherapy may be associated with an increased rate of post-surgical complications up to 21.4% [209] and up to 31% when bevacizumab is included [210]. Additionally, in locally recurrent rectal cancers, reports of response in the primary site to systemic palliative chemotherapy are approximately 50% of that observed in metastatic sites [211].

Another American study used SCPRT followed by a delay when 4 courses of mFOLFOX6 were administered to patients with LARC. This study reported substantial histopathological down-staging to ypT0-2 in 75% of patients and to ypT0 in 30% of cases [212]. In the Dutch M1 phase II trial, patients presenting with rectal cancer and synchronous resectable metastases were treated with SCPRT followed by 6 cycles of capecitabine and oxaliplatin (Xelox) plus bevacizumab. Compliance to CT was very high and 90% received ≥4 cycles of treatment. In total, 36/50 (72%) of patients eventually underwent radical surgical treatment [213]. A randomised trial in patients with fixed cT3 or cT4 primary or locally recurrent rectal cancer also received this sequence (SCPRT and mFOLFOX4) and achieved a microscopically radical resection (i.e. an R0 resection as a primary endpoint) in 77% and a 16% ypCR rate with this schedule [214]. Interestingly, the arm delivering SCPRT and mFOLFOX4 showed a similar DFS to the standard CRT, but a significant improvement in overall survival, suggesting an immune effect. These results have led to 'the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation' (RAPIDO) trial. Patients were randomised to SCPRT followed by 6 cycles of Xelox and then TME or fluoropyrimidine-based preoperative long-course CRT followed by TME. Postoperative adjuvant chemotherapy was optional. The trial completed accrual in 2016 and results are awaited [215].

Neoadjuvant Chemotherapy Alone (No RT)

Early use of neoadjuvant chemotherapy at full systemic doses may be more effective at destroying micrometastatic disease and thus reducing the risk of distant failure in patients with LARC, where the predicted risk of metastatic disease is high at 30–50% [8, 216–218]. Peng et al. describe a lower cause-specific survival for such patients when they receive postoperative RT compared with pre operative RT or no RT at all [219]. Neoadjuvant chemotherapy offers an alternative to CRT in LARC patients with potential advantages which include rapid relief of symptoms, better compliance when compared with chemotherapy administered adjuvantly, avoidance of long-term radiation toxicity (and possibly reduced times to stoma reversal) and the possibility of measurement of any early *in-vivo* response to systemic treatment. Data from Greccar 4 raises the suggestion that NACT may contribute to greater T-downstaging and reduce the risk of an R1 resection [220]. Conversely, neoadjuvant chemotherapy alone could have the disadvantage of selecting out radio-resistant clones and inducing accelerated repopulation [221].

Two French randomized trials are exploring neoadjuvant chemotherapy prior to CRT. The Phase III trial Prodige 23 compares preoperative CRT alone with induction CT (6 cycles of Folfirinox) followed by CRT and surgery for patients with resectable high-risk LARC (NCT01804790). GRECCAR 12 is a further phase III trial comparing 4 cycles of induction Folfirinox followed by CRT and either conventional TME surgery or local excision (depending upon response) versus the standard CRT and surgery or local excision for cT2or cT3 tumors with a primary end point of organ preservation/absence of stoma (NCT02514278).

The evidence for the efficacy of neoadjuvant chemotherapy alone in LARC rests with a single randomised phase III study and six small single-arm studies and a very small retrospective case series [222]. These studies have shown that preoperative chemotherapy results in good overall response rates (62.5–93.7%) with a pCR ranging from 3.8% to 33.3%. The R0 resection was high (90–100%) and the compliance rate was between 72% and 100% with Grade 3–4 toxicities ranging between 2.3% and 39%. The OS and DFS at 4/5 years ranged from 67.2% to 91% and 60.5% to 84%, respectively. Studies with more dose-intense therapy and multiple agents (intravenous and/or oral) followed by surgery have shown better tumour response rates [223–225].

PROSPECT trial is running in the USA and Canada (NCT01515787) sponsored by the Alliance for Clinical Trials in Oncology and is randomising. Those in the experimental (FOLFOX) arm will be assessed after 6 cycles and if there is <20% tumour shrinkage on ERUS/MRI these patients will receive standard CRT prior to definitive surgery. Patients with T4 tumours and a positive CRM are excluded. The primary endpoint is complete resection rates (phase II portion) and disease-free survival/time to LR (phase III portion). The eligibility for this trial includes patients with exceptionally good outcomes [226]. With a high proportion of low risk patients, results are likely to show both options are associated with low rates of local

recurrence thus supporting omission of radiotherapy for responding patients, with consequent reduced toxicity.

Conclusions

Rectal cancer management differs from that of the colon. The diversity of tumour biology, the presence or absence of molecular markers, variability in MRI staging, the numerous options for chemotherapy and CRT/SCPRT regimens all make a simple and single universal therapeutic treatment algorithm difficult to define. Validated, reliable and reproducible biomarkers are still lacking which predict response to CRT and which assist in the calculation of a risk profile of individuals so as to maximize local control and minimize distant relapse. Systemic chemotherapy at systematically active doses, delivered earlier in the patient's treatment needs to be tested in large scale trials. There is currently an insufficient understanding of the precise mechanisms of action of many targeted agents, along with their innate and acquired resistance mechanisms and their effects on tumour tissue and surrounding normal tissues particularly when RT is used concomitantly. New targets such as c-MET, the PI3 kinase, and Wnt pathways need to be systematically explored, as well as the role of immune-checkpoint inhibitors. Over-staging remains common and hence both under or overtreatment are potential traps for the oncologist. Recent data from Korea show that for low- and middle-third cT3a and cT3b tumours with an uncompromised MRF (according to MRI), that there is a low local recurrence rate and excellent 5 year DFS (89%) whether mesorectal nodes are involved or not. In these circumstances CT alone and CRT are likely to have an equal but minimal effect. In contrast, for higher-risk patients with T3c/d EMVI and a threatened CRM, induction CT prior to CRT has not adversely impacted local control and has clearly been associated with a better compliance and lower toxicity than postoperative treatment.

An improved molecular understanding of rectal cancers (perhaps differentially above and below the peritoneal reflection) is required in order to evaluate prognosis and chemo- immuno-responsiveness. In general, rectal cancers have less microsatellite instability, fewer BRAF mutations, more NRAS and Her-2 (cerbB2) overexpression with less hypermutations than right-sided cancers and a greater association with Wnt, myc and SCR activation. Given these molecular subtype variations, retrospective data may require repeat analyses. Prospective molecular subtyping will also better define the potential responsiveness or resistance to additive immunotherapies. Currently the US National Comprehensive Cancer Network Guidelines endorse a total neoadjuvant approach in high-risk cases (4 months FOLFOX systemic CT upfront, followed by CRT and then surgery) [197]. For LARC patients, the NCT 02008656 trial evaluating disease-free survival and randomising cases post CRT either to induction or consolidation CT and then either TME surgery or non-operative management, will establish the best clinical pathway for these patients and the optimal sequencing of CRT and neoadjuvant therapy.

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Part VII
The Management of Metastatic Disease: An Overview

Chapter 23
Resection of the Rectal Primary Tumor in the Setting of Metastatic Disease

Sarah W. Grahn and Ann C. Lowry

In 2014, The American Cancer Society estimated that 40,000 new cases of rectal cancer were diagnosed [1]. Approximately 15–25% of patients have metastatic disease at the time of diagnosis, with liver and lung metastases being the most common sites [2–5].

Historically, the treatment options were limited for these patients and the prognosis overall was fairly grim. Over the past several decades, however, there have been considerable advances in systemic chemotherapy, the more routine use of biologic agents and in surgical techniques which have translated into tangible improvements in the median survival and in the progression-free survival (PFS), even in those with advanced colorectal cancers. As a consequence, the overall survival of a patient with stage IV colorectal cancer was 20% in the 1980s and 1990s, but more recently, between 2003 and 2009, the 2-year overall survival (OS) was over 40% [6].

A multi-disciplinary approach to these patients is extremely important because of the variety of options available, as well as because of the variability in presentation and the coincident co-morbidities of these patients. Discussion of each individual case at a multidisciplinary conference is recommended [7]. For example, management of a 48 year-old healthy patient with rectal cancer and a solitary liver metastasis will likely be approached differently from an elderly frail patient with multi-site metastatic disease. The patient's symptoms, medical condition and distribution of disease need to be carefully considered.

The treatment planning for these patients has also changed in recent years with the development of effective chemotherapeutic agents. It is well established that systemic chemotherapy can improve the PFS and the OS for many patients with

S. W. Grahn · A. C. Lowry (✉)
Division of Colon and Rectal Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, USA
e-mail: ALowry@crsal.org

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stage IV disease who have an acceptable performance status [8]. Currently, results from phase III trials addressing specifics regarding optimal sequencing of chemotherapy, radiation therapy and surgery are lacking.

Despite this uncertainty, clinical practice is changing. Analysis of the U.S. Surveillance, Epidemiology and End Results database has shown that 45% of stage IV rectal cancer patients underwent resection of the primary tumor from 1988 to 2000 [9]. In recent years, with more effective chemotherapy regimens, there is an increasing trend toward non-operative management of stage IV CRC with less than one-third of the cases undergoing a palliative resection in 2008 [10].

For the purposes of discussion, patients may be divided into individual categories; namely:

- Those patients with potentially curable metastatic disease
- Asymptomatic patients with questionably curable metastatic disease
- Symptomatic patients with metastatic disease
- Patients with incurable metastatic disease and reasonable health and
- Patients with significant medical co-morbidities or extensive burden of metastatic disease for whom palliation is the goal.

Patients with Potentially Curable Synchronous Metastases

The most recent NCCN guidelines recommend treatment based upon whether the circumferential resection margin (CRM) is clear as determined by MRI [11]. If the CRM is clear, systemic chemotherapy is the first treatment followed by either short course radiotherapy (preferred) or adjuvant long course chemoradiation. The patient is then restaged and if appropriate undergoes either staged or synchronous resection of the primary and metastatic lesions. If the CRM is involved, systemic chemotherapy combined with long course radiation, or short course radiotherapy may be recommended first. If systemic chemotherapy is given first, it is followed by chemotherapy with long course radiation. Either version of radiation therapy is followed by systemic chemotherapy. The patient is then restaged and if appropriate undergoes staged or synchronous resection of the primary and metastatic lesions. A European consensus document published in 2014 recommends either resection followed by six months of chemotherapy or 3 months of chemotherapy (especially if multi-site metastasis), resection and then 3 months post-operative chemotherapy. The first option is preferred for primary lesions that are T1-T3 or N0. If the final pathology reveals T3, positive lymph nodes, positive circumferential margins or perforation, then post-operative chemoradiation would be given before completing the chemotherapy. For lesions >T3 or N+ lesions, chemoradiation and 3 months of chemotherapy would be given before surgery. A more recent European expert panel recommended systemic chemotherapy with short course radiation as the preferred treatment but also acknowledged that other combinations are reasonable [12]. In 2014, the NCCN panel eliminated the surgery first option because "they believe that the majority of patients should receive preoperative therapy"

with the goal of eradicating micro metastases. There is acknowledgement that not all patients are candidates for chemotherapy and their care should be individualized. Supporting evidence for this position is not provided.

The necessity of pre-operative chemotherapy is still controversial for patients with early primary lesions and a solitary metastasis, however, it would typically be offered for the majority of patients with a primary lesion <T3 (and N0) with a metastasis. The next decision is then usually whether to perform staged or synchronous resections assuming that the metastasis is in the liver; options which are considered Chap. 24.

For patients with primary T3 or T4 or N+ lesions, chemoradiation may follow the initial 3 months of chemotherapy depending upon the response of the primary lesion. If not given before surgery, it may also be considered post-operatively if the risk factors for local recurrence are identified within the pathologic specimen [13, 14].

Further confounding this decision is the timing and the use of radiation. In this respect, Huh et al. published a retrospective review of 140 consecutive Korean patients from 1994 to 2010 with metastatic and locally advanced rectal cancer [15]. All patients underwent surgery but about 50% had either pre or post-operative chemoradiotherapy. Local recurrence was less for those receiving preoperative CRT when compared with postoperative CRT but neither group was significantly better off than the no radiation group. There was no difference in overall or disease-free survival with either pre- or post-operative CRT compared with surgery alone however, improvements in local recurrence-free survival with preoperative RT may suggest that a significant proportion of the patients die before a local recurrence occurs. Whereas a number of retrospective studies have shown that postoperative CRT does not improve OS in patients with metastatic rectal cancer [16–18], this is the first study to examine the effect of preoperative CRT in these stage IV rectal cancer patients.

Other studies have shown that preoperative radiation sandwiched with neoadjuvant chemotherapy (chemotherapy → radiation → chemotherapy) offers a survival benefit but only in those who can undergo a subsequent curative resection of the primary and a metastasectomy [18]. This study supports the concept that patients with locally advanced rectal cancer and limited metastatic disease are the best candidates for chemoradiation. If metastatic disease is more extensive, then survival may not be long enough for local recurrence to be an issue. Adjuvant chemotherapy will still be used in such cases even with curative intent resections (primary + metastasis) since further distant metastases are the most common manifestation of failure in stage IV rectal cancer cases. This would further explain why there is no beneficial effect of pelvic irradiation on either OS or DFS [19].

One concern about the use of chemoradiation is that the chemotherapy used for radiosensitization is not as effective systemically. If survival is the primary concern, then chemoradiation may delay effective systemic treatment. A recent phase II trial addressed that issue with a program of alternating systemic chemotherapy and chemoradiation [20]. The study was designed to determine feasibility. The majority (92%) of patients completed the 12-week treatment and response rates were encouraging. Further studies are needed to determine if this type of regimen would allow effective systemic and local therapy to be combined. The competing elements

of treatment create a dilemma concerning local treatment to avoid uncontrolled pelvic disease or the need for emergency surgery (for obstruction and/or perforation) or to commence first line systemic CT. Any local therapy will also significantly delay the commencement of palliative chemotherapy, even delaying the possibility in borderline performance status of ultimate metastasectomy. Future studies will need novel scheduling in order to address local and systemic problems induced by the advanced rectal cancer concurrently. The use of CT in the RT-free window will potentially reduce the degree of acceleration of the cell population which may have been induced after initial RT. Shorter, intensive CRT regimes may be associated with a lower toxicity whilst maintaining efficacy.

One advantage to chemoradiation therapy is the possibility of a complete clinical response locally which occurs in 15–20% of patients [8, 21]. Prolonged intervals between treatment and surgery and additional chemotherapy have resulted in even higher levels of response [22–25]. With the information currently available, the general recommendations for care of this group are shown in Fig. 23.1. Patient preferences and individual patient factors may alter this treatment plan.

For asymptomatic patients with questionably resectable metastatic disease, the NCCN guidelines recommend chemotherapy using regimens with "high response rates" [12]. Re-evaluation for potential resection should occur in 2 months time and then every 2 months as long as the chemotherapy is continued. The EURRECA document states that the current standard is 3–6 months of induction chemotherapy [13]. If re-evaluation finds that the metastatic lesions have become resectable, local treatment should be based upon local staging. Short-course radiation therapy is preferred but long-course chemoradiation should be considered if the circumferential margin is threatened. The concern here is that chemotherapy as administered with radiation has limited systemic impact. Following surgery, patients should receive postoperative chemotherapy for a total of 6 months of treatment. If re-evaluation finds that metastatic disease remains unresectable, then chemotherapy should be changed to second line with another re-evaluation planned after 3 more months. For larger liver metastases, selective portal vein ligation or embolization could be considered.

Given that the goal of treatment is longevity and quality of life, systemic chemotherapy is the first line treatment for these patients. Benefits of upfront chemotherapy include the ability to down stage metastases from unresectable to potentially

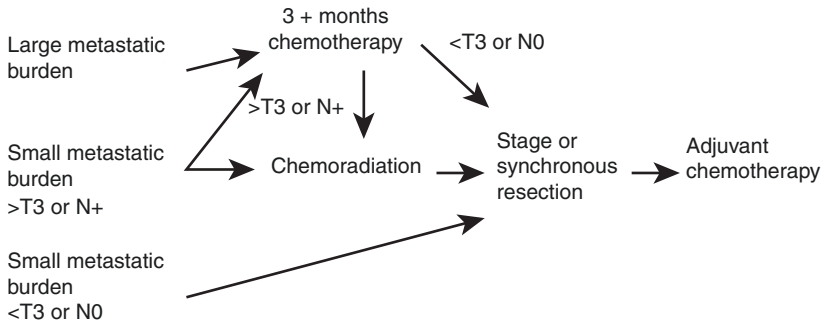

Fig. 23.1 Suggested management flow chart for patients presenting with potentially curable metastases from rectal cancer

resectable. With prompt initiation of systemic therapy, approximately 12–30% of patients may convert to resectable disease that is suitable for complete surgical removal of the primary and metastasis [26–29]. There have also been reports of up to 7% complete pathological response after preoperative chemotherapy alone for stage IV rectal cancer [28].

Patients who are able to undergo complete surgical resection of their colorectal liver metastasis and the primary lesion have a 30–50% survival at 5 years [30]. In this subset of patients, the next decisions are whether they should have a combined procedure with resection of both the primary and metastatic disease as well as the use of pre-operative radiation.

While care must be carefully individualized, a general plan is outlined in Fig. 23.2 for this subset of patients.

Patients with Unresectable Metastases

For those with metastatic disease, over 75% are considered unresectable [31]. The goal of treatment for these patients is to balance length of survival, palliation of symptoms and optimization of quality of life. Treatment decisions should be based upon whether the patient is experiencing symptoms from the primary lesion.

For asymptomatic patients, the NCCN guidelines recommend systemic chemotherapy with periodic assessment for resectability of the metastatic disease when appropriate. The NCCN panel believes that risk of resection of the primary outweighs any potential benefit [12]. The EURRECA group recommends an "escalation strategy" for chemotherapy for completely asymptomatic patients [13]. Intensive (maximal response) chemotherapy is recommended for patients with symptoms related to the metastases. For patients who are symptomatic from the primary lesion, avoidance of surgery is recommended. Radiation therapy, stent placement and diverting stoma should be considered to alleviate symptoms as appropriate rather than surgery. Unless there are specific indications for acute management of the primary in this setting, provided that patients are under surveillance the majority will not require emergent surgery for intestinal obstruction and/or perforation [32]. Although some studies have demonstrated a survival benefit for primary resection [33], the

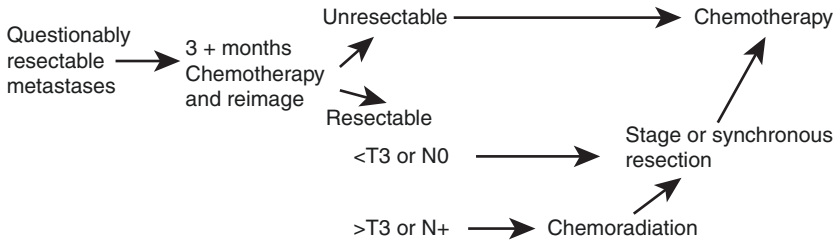

Fig. 23.2 Suggested management flow chart for patients presenting with questionably resectable metastases from rectal cancer

data are biased towards patients with a better performance status and better prognosis (less metastatic sites involved).

In practice there is still discussion about the best option. Resection of the primary tumor in those with unresectable metastatic disease is often considered in cases where the primary tumor is symptomatic. Ten to thirty percent of patients undergo surgery for the primary at the time of diagnosis [34, 35]. The standard indications for resection of the primary include perforation, obstruction not amenable to stenting and refractory bleeding. If the sole indication for surgery is bleeding, radiation is an alternative treatment [36].

Although expert panels recommend avoiding upfront surgery in favor of systemic chemotherapy, there remains controversy in those patients with incurable stage IV disease and minimal to no symptoms from the primary tumor where the patient is healthy enough to undergo surgery. The literature in this circumstance is very mixed (Table 23.1) [34, 35–49].

In this patient population with an overall but variable mean survival of 16–75% [9] a frank discussion with the patient is necessary so as to lay out the potential risks of leaving the primary in place and proceeding with upfront chemotherapy versus the risk of upfront surgery and the potential complications that may delay or even preclude the initiation of systemic therapy.

Proponents of upfront resection also cite the risks of an intact primary lesion including future obstruction, bleeding, pelvic pain and the need for emergency surgery or other intervention whilst on systemic therapy. Limited, mostly retrospective data are available but it may help guide discussions with the patient.

Table 23.1 Summary of studies favoring or not favoring resection of primary tumor first

Reference	Study type/design	Tumor site
Favors resection		
Ruo (2003)	Retrospective	Colon & rectum
Konyalian (2007)	Retrospective	Colon & rectum
Galizia (2008)	Retrospective (case matched)	Colon& rectum
Bajwa (2009)	Retrospective	Colon & rectum
Venderbosch (2011)	Retrospective of 2 RCTs	Colon & rectum
Karoui (2011)	Retrospective	Colon
Verberne (2012)	Retrospective	Colon & rectum
Ferrand (2013)	Retrospective	Colon & rectum
Does not favor resection		
Scoggins (1999)	Retrospective	Colon & rectum
Tebbutt (2003)	Retrospective	Colon & rectum
Michel (2004)	Retrospective	Colon & rectum
Benoist (2005)	Retrospective	Colon & rectum
Seo (2010)	Retrospective	Colon & rectum
McCahill (2012)	Retrospective	Colon & rectum
Yun (2014)	Retrospective/propensity score matching	Colon & rectum

RCT randomized controlled trial

In this respect, the rates of bowel obstruction whilst on chemotherapy for stage IV colorectal cancer where there is still an intact primary, range from 6% to 29% with a mean of 22% [10, 29, 48–51]. In 2003 Tebbutt and colleagues sought to define the rates of intestinal complications with chemotherapy in patients with metastatic colorectal cancer where there was still an intact primary. The incidence of peritonitis, fistula formation and intestinal hemorrhage were all low at 2.4%, 3.7% and 3.7% respectively [45]. Obstruction occurred in 13% of patients with an intact primary. Of interest, similar raw numbers of intestinal obstructions were reported in the cohort who underwent initial palliative resection of the primary, underscoring the difficulty in discerning if the obstruction is at the level of the tumor or elsewhere within the peritoneal cavity. Tebbutt concluded that the incidence of major intestinal complications is low amongst patients with synchronous CR metastasis and an intact primary. As expected, obstruction is more common in those with peritoneal and omental disease.

Another risk of leaving the rectal cancer primary intact is that symptoms of local disease may be more pronounced and the need for a stoma more likely. Between 14% and 60% of patients without resection of the primary may require proximal diversion or other intervention whilst on palliative chemotherapy [35, 52–54]. Sarela et al. reported a 14% incidence of late symptoms from the unresected primary rectal cancer [55].

With modern combination chemotherapy regimens for unresectable stage IV colorectal cancer, Poultsides et al. reported that the overall incidence of primary tumor-related complications was only 15% [29]. Only 6% required surgical intervention, with an additional 9% requiring non-operative interventions such as stenting or radiation. Another similar study found that 22% of patients undergoing palliative chemotherapy required intervention and that about 50% required operative intervention [10, 49]. In this Korean study, the location of the primary tumor in the rectum and a tumor size >5 cm both independently predicted the need for intervention on multivariate analysis. Michel and colleagues reported that 21% of patients in a non-resection group required intervention for obstruction [46] and that a location of the primary in the rectum increased the risk.

While the incidence is low, the mortality rate for urgent surgery is significant at 12.5%. Temple and colleagues found that the post-operative mortality increased from 9% to 26% when surgery was performed after chemotherapy [56]. In addition, perforation and fistula formation each occur at a rate of 11% and may require urgent diversion or other intervention where emergency surgery in this group has a significantly higher mortality and morbidity, suggesting that a balance needs to be made between the low risk of complications in an observed group and that of emergent or semi-emergent surgery [54]. Monitoring of the primary either with endoscopy or radiologic imaging may reduce the need for urgent surgery [57].

Pelvic pain can also have a significant impact on quality of life in patients with locally advanced rectal cancer. Studies show significantly less pelvic pain in those who had undergone a resection of the primary, 4% vs. 15% [52]. There is also less pelvic sepsis in this resection group, 9% vs. 14%. Others have also reported fewer pelvic symptoms following resection [58, 59] although these reports, however, predate modern chemotherapy and radiation therapy advances.

The Mortality of Urgent Surgery: Stents and Stomas in Stage IV Rectal Cancer Cases

As already stated, one argument for elective resection of the primary is to avoid urgent surgery. About 15% of patients on aggressive chemotherapy even with radiation will go on to need palliative intervention for obstructive symptoms [59]. In this regard, there is a significant increase in 30 day post-operative mortality when the results of elective surgery are compared with emergent surgery, 2.5% vs. 10% [60].

Given the approximate 15% mortality rate associated with emergency surgery for left-sided colorectal cancers, decompression with minimally invasive techniques such as stenting has been studied as an alternative [61]. The success overall of stenting is highly variable, but some series have reported as high as a 40% perforation rate in those with left-sided colorectal cancers treated with palliative stenting [62]. A recent meta-analysis of studies comparing stenting with emergency surgery found no difference in hospital mortality or overall morbidity and recommended that stenting be considered cautiously as an alternative to surgery [63]. However the European and American Societies of Gastrointestinal Endoscopy recommend self-expanding stent placements as the preferable treatment in a palliative situation except in patients being treated with antiangiogenic drugs [64]. In a recent randomized controlled trial comparing stent placement with emergency surgery for incurable large bowel obstruction, about 20% of patients had rectal cancer [65]. Stent insertion in this Australian study was successful in 73% of patients and overall, the stent group had fewer stomas, a lower 30 day mortality and better measurable quality of life parameters. The median survival was equivalent in the two groups (5.2 months surgery *vs.* 5.5 months stenting).

Concerns with resection of the primary in the setting of unresectable metastasis include the possible 40% risk of postoperative morbidity [42, 66] and the attendant 0–8% peri-operative mortality rate [42, 52, 66, 67]. Nash and colleagues from Memorial Sloan-Kettering reported a 1% perioperative mortality in this group with a 15% major peri-operative morbidity rate with resection of the rectal primary without neoadjuvant radiotherapy in their series [66]. A recent study suggests that laparoscopic versus open resections result in fewer overall complications [68]. Of consideration is the fact that postoperative complications can delay and prevent the administration of systemic chemotherapy in 12–40% of cases [42, 66]. Delays in adjuvant chemotherapy for rectal cancer are strongly influenced by postoperative complications. Median overall survival is significantly worse in those that had a greater than 2 month delay in starting adjuvant chemotherapy [69].

Anastomotic leaks specifically also have a complex impact on survival. In a study of 123 patients with metastatic rectal cancer undergoing resections, anastomotic leaks occurred in 6.5% [70]. The 3-year overall survival was significantly worse (32% *vs.* 72%) in patients with a leak. This finding may relate to a delay of systemic chemotherapy use for over 2 months in 50% of the patients. Kleepsies and colleagues reported anastomotic leaks in 24% of rectal cancer patients, although only 6.5% required re-operation [71]. Post-operative treatment was administered

in 72.6% vs. 91.9% of patients without complications. In many cases, the surgical resection of a rectal cancer in the setting of unresectable metastatic disease results in a colostomy (between 20% and 66% of series) [66, 71].

Survival

When assessing the impact on survival for patients with CRC and unresectable metastases, there are limited data comparing initial primary tumor resection *vs.* upfront chemotherapy. The studies are not randomized and most represent retrospective single institution reports. A Cochrane review in 2012 found that "resection of the primary tumour in asymptomatic patients with unresectable stage IV colorectal cancer who are managed with chemo/radiotherapy is not associated with a consistent improvement in overall survival. In addition, resection does not significantly reduce the risk of complications from the primary tumour (i.e. obstruction, perforation or bleeding). Yet there is enough doubt with regard to the published literature to justify further clinical trials in this area" [72].

Theoretically, the removal of the primary lesion would reduce the total tumor burden, potentially making chemotherapy more effective on the residual tumor. The literature is in this respect, however, mixed in terms of the survival benefit of resection of the primary. A recent meta-analysis included retrospective and cohort studies within the past 15 years involving 44,226 patients with either colon or rectal cancer where two-thirds of the patients underwent resection [73]. The study demonstrated a survival advantage with resection of the primary in CRC when compared with chemotherapy alone. Patients who had a resection lived a mean of 6 months longer, 95% CI 5.0–7.8; $P < 0.001$ [31, 60]. Those undergoing resection were more likely in this cohort to have metastatic disease confined to the liver, (usually as single metastases) as well as tumors in the colon and not the rectum. Those with advanced rectal cancer were more likely to receive palliative surgical procedures such as a stoma rather than resection of their primary in this retrospective analysis. In this approach, there is an inherent selection bias because of the retrospective nature of the study, as surgery may be offered more commonly to patients with a better performance status and lower disease burden. Consequently this data should be viewed and interpreted with caution. Two other reviews have also found that resection provided better or equivalent survival but these did not find that the tumor location in the colon or rectum had any significant impact [31, 60].

One of the studies included was a retrospective analysis of the data in two phase III trials of various chemotherapy regimens for metastatic colon cancer patients [40]. The patients undergoing resection were compared with those who were unoperated. In both analyses, the median overall survival (16.7 *vs.* 11.4 months, respectively; $P < 0.001$) and progression-free survivals (6.7 *vs.* 5.9 months, respectively; $P = 0.04$) were better in the resection groups.

There are a few studies specifically examining rectal cancer with variable findings regarding the impact on survival of resection the primary. Verberne reported a

consecutive series of 88 patients between 2002 and 2006 with stage IV rectal cancer [42]. Thirty percent of the cohort underwent resection. Those who had resection of the primary were compared with patients with an intact primary who received chemotherapy or supportive care only. Those who underwent palliative resection had a significantly better survival than those unoperated (OR 0.38 95% CI *vs.* 0.173–0.831, respectively). In this study there was a 38% peri-operative morbidity but no attendant 30-day mortality. Other studies have not demonstrated a survival advantage with resection of the rectal primary [45]. Statistical techniques have been used to manage potential biases in these reports where after propensity score matching, Yun et al. has shown that resection of the primary was not associated with an improvement in overall survival [10, 27].

Both the extent of metastatic disease and the response to initial chemotherapy are strong and independent determinants of prolonged survival in patients with metastatic rectal cancer [66]. In a study by Nash et al. from the Memorial Sloan-Kettering Cancer Center, greater than 50% hepatic replacement and more than 1 comorbidity were independent determinants of postoperative morbidity. In a similar study by Kleespies and colleagues from Munich, survival was impacted by T4 or node positive disease, >50% extent of hepatic replacement, local tumor clearance (R0/R1-2) and failure of administration of postoperative therapy, suggesting that in these higher risk cases that surgery may actually be contraindicated [71].

Conclusions

The management of the primary rectal tumor in patients with unresectable metastases is challenging. Finding the appropriate strategy to balance the future risk of symptoms from an intact primary with the morbidity of surgical resection can be difficult. Based upon the limited data available, the approach to each patient must be individualized and should be discussed with a multidisciplinary team. Resection or diversion should be considered for symptomatic patients. For those asymptomatic patients with widely disseminated disease who are likely to remain unresectable, aggressive chemotherapy is recommended. That recommendation is made understanding that approximately 15% of patients may go on to become symptomatic and need intervention including focused radiation, diversion or stenting. Patients with Stage IV rectal cancer who remain unoperated require close monitoring so as to avoid the need for emergency surgery for complications such as obstruction and/or perforation, both of which may in advanced metastatic disease have a prohibitive morbidity and mortality. For those patients with more limited metastatic disease and a good performance status, upfront chemotherapy is used to assess tumor responsiveness. If there is a favorable response to chemotherapy and the patient transitions to a potentially resectable situation, the primary lesion should then be treated as in a patient without metastatic disease, including the use of neoadjuvant chemoradiotherapy when appropriate. Whether resections should be synchronous or staged for hepatic metastatic disease in

particular is discussed elsewhere in this book section. Peritoneal disease, the extent of liver involvement and the performance status are all factors that may limit a patient's benefit from surgery and which increase the morbidity and make the recommendation for resection less likely. There are ongoing randomized controlled trials such as the multicenter Spanish NCT02015923 trial comparing surgical resection and postoperative CT (without specific protocol) with CT alone [74] which will hopefully provide clearer guidance for decision making on these complex patients. Recently a clinical trial conducted at University College Hospital London has completed, examining overall survival in asymptomatic stage IV CRC cases treated with CT alone or with resection of the primary + CT. The results at the time of writing remain unpublished (NCT01086618; http://clinicaltrials.gov).

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Chapter 24
Modern Management of Hepatic Metastatic Disease

Christopher J. LaRocca and Eric H. Jensen

Introduction and Natural History

Colorectal cancer is the third leading cause of cancer deaths in both men and women with 136,830 new cases in the United States estimated to be diagnosed in 2014 [1]. For individuals diagnosed with colorectal cancer, approximately 20% of patients will have metastatic disease at the time of initial diagnosis [2]. Despite the overall incidence of colorectal cancer declining, the number of patients presenting with metastases has remained relatively unchanged. In multiple population-based studies, the incidence of synchronous liver metastases was reported to be 14–18% [3–5]. Similarly, on a population level, the rate of metachronous liver metastases was approximately 12–14% at 3 years [3, 4]. The liver is the most common site of distant colorectal metastases and disease is limited to this site in at least one-third of the patients [6]. Overall, approximately 50% of patients will develop liver metastases at some point during the course of their disease.

If left untreated, patients with liver metastases from colorectal cancer have a median survival of approximately 6–12 months, although some studies report survival up to 21 months [7–9]. At initial presentation, 15–20% of all patients with colorectal liver metastases will be candidates for a resection [10, 11]. However, for those who are able to under surgical resection, where the reported 5-year survival rates can exceed 50% in highly selected patient populations [12]. Importantly, as care has improved, so has there been improvement in the morbidity and mortality following these procedures. Modern series have documented mortality rates of less than 1% for carefully selected patients [13–15].

It is clear that the advent of improved chemotherapeutics, enhanced imaging, optimized surgical techniques and perioperative care and improved patient selection has markedly advanced the treatment of colorectal liver metastases.

C. J. LaRocca · E. H. Jensen (✉)
Department of Surgery, University of Minnesota, Minneapolis, MN, USA
e-mail: jense893@umn.edu

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While the natural histories, treatments and sequencing of multimodality therapy differs quite markedly for colon as opposed to rectal cancers, there is a paucity of data regarding the optimal management of liver metastases specifically from rectal cancer. Most of the existing literature combines outcomes for colon and rectal primaries and the treatment for the liver metastases does not differ much depending upon the primary tumor site. It is for these reasons, that the chapter will include discussion of liver metastases from colon and rectal cancers combined.

Medical Management

Systemic therapy is a critical component of care for individuals with metastatic disease and the medical management of colorectal liver metastases has changed greatly over the recent years as newer and improved chemotherapeutics and biologic agents have been developed and approved for usage. This issue is covered elsewhere in greater detail in this book (Chap. 22).

Chemotherapy for Resectable Disease

Up until the late 1990s, 5-flurouracil (5-FU) was the main chemotherapeutic agent used for the treatment of metastatic colon cancer. Even when 5-FU is combined with leucovorin, response rates are only on the order of 20% [16]. It was not until the addition of oxaliplatin and irinotecan to the existing regimens that drastically improved response rates were seen, sometimes exceeding 50% [17, 18]. As the development of new chemotherapeutics continues, it is likely that the response rates and outcomes will continue to improve.

It is unclear what the optimal scheduling of chemotherapy should be for patients with resectable disease. Perioperative chemotherapy plus surgery has been compared with surgery alone for liver only colorectal metastases and the group receiving chemotherapy and surgery demonstrated an increase in progression-free survival [19]. However, overall survival remains unchanged [20]. A recent retrospective study demonstrated that there were no significant differences in overall survival outcomes between groups treated with perioperative chemotherapy and solely adjuvant chemotherapy [21].

Some of the benefits of neoadjuvant chemotherapy include the ability to assess the degree of response to therapy and the identification of patients whose disease progresses during chemotherapy and which may have particularly aggressive tumor biology. Additionally, metastatic colorectal cancer is a systemic disease and preoperative chemotherapy ensures that patients receive some level of systemic therapy in the event that there is a complication from surgery that may later preclude the use of additional chemotherapy. The main downside to neoadjuvant therapy is the risk for chemotherapy-induced liver toxicity, which can affect surgical planning and

outcomes. For patients who do receive neoadjuvant therapy, it should be of limited duration (typically 2–3 cycles) and they should undergo serial radiologic assessments to ensure optimal surgical planning and timing.

Chemotherapy for Unresectable and Borderline Resectable Disease

Upon diagnosis of colorectal liver metastases, some patients fall into the categories of unresectable or borderline resectable disease. For these individuals, chemotherapy is the initial first-line therapy.

Multiple studies have used various "downsizing" or "conversion" chemotherapy regimens to enable patients to undergo surgical resection, with success rates varying from 13% to 50% [22–26]. For those patients with initially unresectable disease where the tumors regress and who are then able to undergo resection of their liver metastases, the 5-year overall survival rates have ranged from approximately 30% to 40% and up to 60% in selected patients [22, 25, 27, 28]. It is important to note that these figures are similar to those of patients with initially resectable disease suggesting that it is the surgical resection of disease that actually confers the survival benefit.

Despite undergoing multiple cycles of chemotherapy, some of these patients will still not be candidates for surgical resection. For these cases, survival ranges from 15 to 20 months depending upon the chemotherapeutic regimen [17, 18, 29, 30]. When 5-FU, leucovorin, oxaliplatin, and irinotecan were used for patients with unresectable disease, a median survival of 22 months was reported [23].

Additionally, targeted biologic agents such as cetuximab (chimeric monoclonal antibody – epidermal growth factor receptor inhibitor) and bevacizumab (recombinant monoclonal antibody – vascular endothelial growth factor inhibitor) have been employed with increasing frequency in recent years. When combined with 5-FU, leucovorin, and irinotecan, cetuximab resulted in an increased response rate and overall survival for patients whose tumors were wild type for the KRAS proto-oncogene [31, 32]. Cetuximab, in conjunction with modern chemotherapeutic regimens, has also been shown to increase the number of patients able to undergo resection [33, 34]. Additionally, bevacizumab has been shown to increase overall survival when combined with 5-FU, leucovorin, and irinotecan [35].

Chemotoxicity

The effectiveness of newer chemotherapeutics has allowed more patients to proceed to resection and has prolonged their overall survival. Despite these benefits, modern-day chemotherapies are not without potential complications.

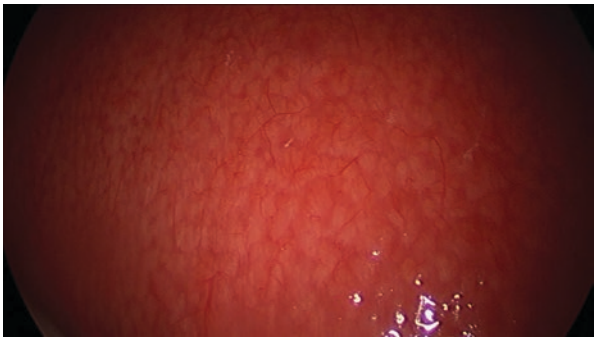

Fig. 24.1 Steatosis following neoadjuvant chemotherapy
This image is from a patient who was treated with a regimen containing 5-FU and subsequently developed liver parenchyma with this fatty appearance, a hallmark of steatosis

Non-alcoholic fatty liver disease (NAFLD) describes a range of pathologic conditions within the liver. The most benign of these disorders is steatosis (Fig. 24.1), which is simply the deposition of triglycerides in the cytoplasm of hepatocytes [36]. 5-FU belongs to a class of drugs known as fluropyrimidine anti-metabolites and it has been linked to the development of steatosis. Studies have demonstrated the fatty changes visible on computed tomography following treatment with 5-FU [37]. While these changes have not affected the overall mortality following hepatic resection, there has been a significant impact upon morbidity and in particular infectious complications [38]. In particular, 62% of patients with marked steatosis had a major complication when compared to 35% of patients who had no steatosis ($p < 0.01$) [38]. Also, 43% of patients with marked steatosis had infectious complications compared with 14% of patients with no steatosis ($p < 0.01$) [38].

Steatohepatitis is a more severe form of NAFLD and it is characterized by not only lipid deposition but also hepatocyte injury and inflammation [36]. Irinotecan is a topoisomerase I inhibitor that has been implicated in its development [39, 40]. In the series by Vauthey et al., 20.2% of the 94 patients who received irinotecan developed steatohepatitis [40]. For patients undergoing hepatic resection after neoadjuvant chemotherapy, steatohepatitis has been shown to impact mortality. In a multicenter study, patients with steatohepatitis had a 90-day mortality of 15% compared with 2% for those who had not developed this disease (Odds ratio 10.5; $P = 0.001$) [40].

Hepatic sinusoidal obstruction syndrome (SOS) is caused by an injury to the sinusoidal endothelial cells, which then results in a loss of wall integrity and sinusoidal congestive obstruction [41]. SOS can also result in a bluish discoloration of the liver parenchyma (Fig. 24.2). Historically, SOS was a rare occurrence. However, it has been increasingly reported with certain modern-day chemotherapeutic agents such as oxaliplatin, which is a platinum-based agent that mediates its effect through direct DNA damage. In the context of pre-operative chemotherapy for patients with colorectal liver metastases, multiple series have reported an association between oxaliplatin and sinusoidal injury [40, 42]. It has been shown that up to 78% of patients treated with oxaliplatin can have some degree of sinusoidal alterations [42].

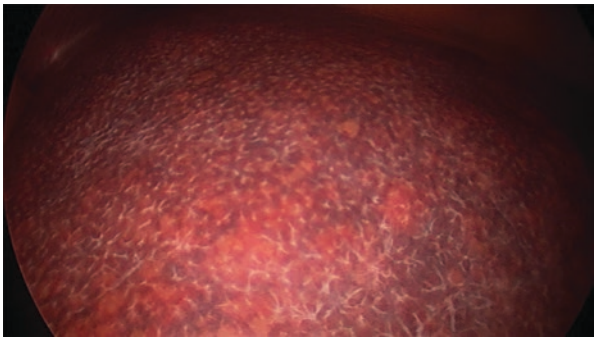

Fig. 24.2 Sinusoidal obstruction syndrome (SOS) after pre-operative chemotherapy
This image is from a patient who received chemotherapy with cisplatin and subsequently developed SOS, as evidenced by the characteristic "blue liver" appearance

Furthermore, pre-operative chemotherapy with oxaliplatin and its associated hepatic vascular changes have been noted to cause a significant increase in the amount of red blood cell transfusions required during surgery [43].

Following the diagnosis of colorectal liver metastases, patients historically received up to 6 months of chemotherapy before seeing a liver surgeon. In current multidisciplinary practices, patients are seen in surgical clinics much earlier during their treatment course. It is unclear what is the optimum length of chemotherapy before surgery, but it is important to note that increased length of chemotherapeutic regimens have not been shown to have an improved effect on pathologic response, but they have been shown to increase toxicity [44]. For this reason, neoadjuvant regimens should be used judiciously.

It should also be noted that the time interval between the completion of the neoadjuvant therapy and the surgical resection can have an impact on the surgical outcomes. When this time period is <4 weeks there can be an increasing likelihood of chemotherapy-associated liver injury as well as an increase in postoperative complications [45, 46]. For these reasons, there should be an interval of at least 4–6 weeks between the completion of chemotherapy and surgery.

Surgical Management

In recent years, the survival outcomes for surgical resection of hepatic colorectal metastases have improved on account of better patient selection, improved chemotherapeutics, advances in surgical technique and progress in perioperative care. Table 24.1 summarizes several notable studies and pertinent survival outcomes, which are measured at the time of surgery [13–15, 47–52].

From these large series of patients, various factors have been analyzed which have potential prognostic significance. Due to the variations in patient characteristics and sample sizes, not all studies have reached the same conclusions. However, there are a few important factors that should be used to guide surgical planning. General principles are provided below in decision making concerning hepatic metastasis resection.

Table 24.1 Survival outcomes following resection of colorectal liver metastases

			Overall survival (%)				Median survival
Author	Year	Number of patients	1 year	3 year	5 year	10 year	(Months)
Scheele	1995	434	–	45	33	20	39.6
Nordlinger	1996	1568	88	44	28	–	–
Fong	1999	1001	89	57	37	22	42
Minagawa	2000	235	–	51	38	26	37.2
Choti	2002	226	93	57	40	26	46
Pawlik	2005	557	97	74	58	–	74.3
House	2010	1037 (era 1: 85–98)	–	56	35	16	–
		563 (era 2: 99–04)	–	65	43	–	–
Vigano	2013	323	93.6	61.7	38.6	–	47.1
Gur	2013	157	89	57	27	–	42.8

Prognostic Factors

Patient and Primary Tumor

In most studies, age and gender have not been shown to have any prognostic significance [13, 15, 47–50]. Like any other major surgical procedure, patient selection should be based upon physiologic performance status rather than the specific age of the patient with several caveats as they apply to hepatic resection.

Similarly, the location of the primary tumor (colon vs. rectum) has not been shown to have any prognostic significance [15, 47, 48, 50], although this is not universally reported [49]. Resection of hepatic metastases improves survival for both sites of disease and therefore the location of the colorectal primary should not influence the decision for liver resection.

Positive mesenteric lymph nodes associated with the primary tumor have a negative impact on survival [15, 47–49]. Although not universally shown, advanced stage of the primary tumor is generally recognized as a negative prognostic factor when considering resection of hepatic metastases. As with other prognostic considerations, the history or presence of a node-positive primary tumor is not a contraindication for surgical resection of metastatic disease, but rather should be used as part of a larger assessment of potential outcomes for the patient.

Size of Metastases

While tumor size (>5 cm) has traditionally been considered a negative prognostic factor and contraindication for surgery, there are recent reports to the contrary. Multiple studies have suggested that tumor size does not significantly impact survival following hepatic resection [13, 48]. Acceptable outcomes have even been reported for patients with tumors up to 12 cm in size [53]. Similar to other prognostic factors, large size of the tumor is not a contraindication for surgical resection, but

should be considered when estimating the potential survival benefit of extended surgery. Unless it impacts on the technical ability to remove the tumor with negative margins, size itself should not preclude surgical treatment.

Number of Metastases

The number of lesions in the liver affects the potential benefit of metastasectomy, and so the first issue to consider with any planned surgery is the ability to effectively treat all areas of disease. Historically, there has been question of the benefit of multifocal resections in patients with more than four lesions in the liver; however, more recently, the number of liver metastases has become less of a contraindication to surgical resection. Multiple studies have suggested that it is acceptable to resect more than four tumors during a single operation [54–56]. There is no clear cutoff for the maximum number of lesions, but the simultaneous resection of 8 or more tumors has been associated with poorer survival outcomes [57]. When considering the resection of multifocal disease, it is paramount that all lesions be completely treated by resection and/or ablation. There is no survival benefit for patients who have incomplete treatment of their disease.

Disease-Free Interval in Metachronous Disease

Multiple authors have suggested that the interval between the resection of the colorectal primary and the appearance of liver metastases (disease-free interval) can have a prognostic significance [47, 49]. It is thought that those liver metastases which appear more quickly may reflect a more aggressive disease biology. Usually, the cutoff timepoint is 12 months, as those patients having an interval of less than 12 months have been shown to have a poorer prognosis [47]. In a study by Tomlinson et al. where they analyzed prognostic factors in cohorts of patients having survived anywhere from less than 2 years to greater than 10 years following treatment of their colorectal liver metastases, a clear trend was observed with respect to the disease-free interval in those patients [58]. When compared with the cohorts with a short overall survival, those with longer survival times demonstrated fewer patients with a disease-free interval of less than 12 months, thereby demonstrating the potential implications of this prognostic factor.

Margins

As is true across many disciplines of oncologic surgery, the inability to achieve a microscopically margin-negative (R0) resection is considered a contraindication to surgery. In recent years, the discussion has focused on what is considered an appropriate width of a negative margin for colorectal liver metastases. Historically, 1 cm

of liver parenchyma was believed to be the minimum for a negative margin. While that width may still be useful to guide surgical planning, the current evidence supports a different recommendation. In a multicenter study of 557 patients, Pawlik et al. reported that the width of the negative margin does not have any significant impact on the surgical margin recurrence [14]. Additionally, the recurrence-free survival was not impacted by the width of the negative margin [59]. These studies demonstrated that upon pathologic analysis of the resected tumor, the surgical margin must be negative, but the width of that negative margin does not matter.

Response to Chemotherapy

The clinical response to chemotherapy has been suggested to be highly predictive of overall survival outcomes. In a study by Adam et al., patients who underwent resection for multiple metastases following disease progression while on chemotherapy had a significantly worse overall survival when compared with those whose disease regressed or stabilized [60]. Similarly, a survival improvement was seen in patients whose disease did not progress while on chemotherapy before undergoing staged resection for synchronous metastases [61]. Another study demonstrated a significantly increased recurrence-free survival in patients who responded to chemotherapy prior to surgical resection [62]. These findings have supported the use of pre-operative chemotherapy as part of a multidisciplinary strategy to improve patient selection for surgery. Recent reports have also suggested that the histologic response to chemotherapy holds some prognostic value. Multiple studies have noted significant survival improvements associated with pathologic responses to chemotherapy [63, 64]. The response to chemotherapy may be one of the most important prognostic factors, as progression during therapy predicts a poor outcome. Many patients receive neoadjuvant therapy and the response to these regimens must be used to guide surgical planning and tailor any future chemotherapies.

Biochemical and Molecular Factors

Carcincoembryonic antigen (CEA) levels greater than 200 ng/mL have been suggested as another negative prognostic factor for overall survival, although this has not been consistently shown across all series [15, 47]. No clear cutoff for CEA has been established, but a markedly elevated value should be used to guide a patient's treatment strategy.

KRAS and BRAF are two proto-oncogenes that have been well-studied for their role in colorectal cancer biology. Mutations in these genes have been implicated in causing resistance to chemotherapies as well as poor prognoses. The mutant form of the KRAS gene has been demonstrated to be an independent predictor of poor overall and recurrence-free survival in patients undergoing resection of colorectal liver

metastases [65]. Additionally, mutations in the KRAS gene are associated with a more aggressive behavior of colorectal liver metastases [66]. The mutant BRAF gene has also been associated with a decreased overall survival when compared with its wild type counterpart in patients who had their metastases resected [67].

Extrahepatic Disease

Extrahepatic disease has long been considered a negative prognostic factor and a contraindication to surgical resection. Elias et al. challenged this notion when they reported a 20% overall 5-year survival following surgical resection of colorectal liver metastases along with one site of extrahepatic disease [68]. Carpizo et al. demonstrated that in patients with a single site of extrahepatic disease and relatively low liver tumor burden, the 5-year survival rate is 27% [69]. Multiple other authors have suggested that extrahepatic disease may no longer be an absolute contraindication for surgical resection where it still may have a role in carefully selected patients [70–73].

Patients with extrahepatic disease have an almost 100% chance of recurrence. Resection is generally not considered curative, but may lead to prolonged survival. From these studies, it can be concluded that in carefully selected patients with a single site of extrahepatic disease and limited liver metastases, it may be reasonable to proceed with surgical resection. The discussion to proceed with surgery in light of extrahepatic disease should not be taken lightly, as the benefit seems to only be in highly selected patients. Generally speaking, individuals with extrahepatic disease should not be considered for resection outside of a clinical trial with all cases discussed as part of a multidisciplinary conference [74]. In a study by Lordan et al. of prospectively assessed patients referred to a specialist hepatobiliary unit over 10 years with separable referring colorectal surgeons sending their MDT cases, the survival rates of those cases referred through the MDT circuit (as opposed to direct referrals to the HPB surgeons) was considerably improved. It is likely that the MDT-referred cases are those with earlier staged disease as their data shows that the median tumor size is smaller with less intraoperative blood loss. This improvement in survival extends out to those cases with up to 3 liver metastases and it is likely also that the use of neoadjuvant therapies is more standardized in these patients.

Clinical Risk Scores

Multiple research groups have proposed different scoring systems for colorectal liver metastases [47, 49, 75]. The scoring system by Fong et al. has been the most widely used and through a multivariate analysis they reported five risk factors which predict disease recurrence following liver resection for metastatic colorectal cancer [47]. These included node-positive primary tumors, a disease-free interval of less than 12 months, more than 1 tumor, a preoperative CEA level greater than 200 ng/

Table 24.2 Negative prognostic factors following liver metastasectomy

BRAF/KRAS mutations
CEA level (>200 ng/mL)
Disease free interval (DFI) of less than 12 months
Extrahepatic disease
Number of tumors (>5)
Poor response to chemotherapy
Positive lymph nodes
Positive surgical margin
Tumor size greater than 5 cm

mL and a tumor size exceeding 5 cm. Whilst clinical scores may not be critical for surgical decision making, they can be used to discuss likely outcomes with patients and their families. They are also helpful for assessing the risks and benefits in high-risk patients who may gain little from surgical resection.

Table 24.2 summarizes several of these aforementioned prognostic factors which may predict outcomes following metastasectomy. Individuals without negative prognostic factors have a 5-year overall survival approaching 60% whereas the survival for those patients with ≥4 factors is around 25% overall [47].

Selection for Surgery

The selection of appropriate candidates for surgery involves numerous considerations, including an evaluation of the aforementioned prognostic factors. Additionally, patients must be considered medically fit for a general anesthetic and a major abdominal operation. They also need to have appropriate pre-operative imaging which will help to guide the decisions of a multidisciplinary team, especially in the setting of patients who may have multiple tumors, large metastases, or extrahepatic disease.

The order of chemotherapy and surgery will be dependent upon the original disease site, timing of the diagnosis of liver metastases and the overall disease burden. For rectal cancers with synchronous liver metastases, all patients will receive neoadjuvant therapy. However, for rectal cancers with metachronous lesions or any colon cancer, patients may or may not receive chemotherapy prior to live-directed therapy. One again, the timing and duration of chemotherapy is best decided in the setting of a multidisciplinary team.

Ultimately, it is the surgeon's responsibility to ensure that a technically sound resection adhering to oncologic principles can be performed, but optimizing patient outcomes is best achieved through shared decision making and careful patient selection.

Pre-operative Imaging

Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound are the four imaging modalities that are commonly used in evaluation of colorectal cancer liver metastases. Each has its

own advantages and disadvantages, as well as clinical situations in which they are most useful.

CT scans are a low cost and widely-available technique to image the liver. The resulting images are easily interpreted by radiologists and hepatobiliary surgeons. For these reasons, it is the most common imaging modality used for staging of many cancers. Colorectal liver metastases are often hypovascular lesions, and so they are best detected on portal venous phase imaging [76, 77]. The sensitivity for detection of colorectal liver metastases has been reported to be upwards of 80%, with a positive predictive value of 96% [77]. However, one of the main disadvantages to CT scans is that they are limited by the inability to accurately characterize lesions less than 1 cm in size [78]. Additionally, the ability to detect metastatic lesions may be decreased in the setting of chemotherapy-induced fatty liver changes [79].

As MRI technology has advanced, the resulting images have demonstrated increasing tissue contrast and spatial resolution for studying colorectal liver metastases. Consequently, MRI is particularly useful when lesions are indeterminate on other imaging modalities or in the setting of parenchymal changes following neoadjuvant therapy [80]. In addition, MRI is best used in a hospital where fellowship trained body-imaging radiologists are available and unfortunately this expertise is not available at all hospitals. MRI is also considerably more expensive than other imaging studies.

Similar to CT scans, the hypovascular nature of colorectal liver metastases makes them most conspicuous on portal venous phase imaging of contrast enhanced MRI, where they appear hypodense when compared with the surrounding parenchyma [81]. Colorectal liver metastases can also demonstrate a peripheral ring of enhancement [82]. It has also been shown that this transient perilesional enhancement on early post-contrast images does correlate with tumor histology of parenchymal changes including desmoplastic reaction and infiltration of inflammatory cells [83].

Two meta-analyses have compared the sensitivity of CT and MRI for detecting colorectal liver metastases and both showed the overall superiority of MRI as well as its increased ability to detect sub-centimeter nodules [84, 85].

Similar to many other malignancies, PET and PET-CT have been widely-used as imaging modalities for the evaluation of metastatic colorectal cancer. Multiple meta-analyses have shown PET to a have a higher sensitivity (compared with CT and MRI) for the diagnosis of colorectal liver metastases on a per-patient basis, which is on the order of 95% [85, 86]. Other benefits include an ability to accurate identify local disease recurrence as well as sites of extrahepatic disease [87]. Unfortunately, the scans are costly and require trained nuclear medicine personnel and equipment that may not be available at all facilities. Furthermore, the role of PET scans within a few weeks of neoadjuvant chemotherapy is unclear as it has been reported that there is an increased rate of false negatives during this time period [88]. In addition, PET-CT imaging has not been found to significantly alter operative planning when compared with CT alone [89].

Ultrasound has the clear benefits of being widely available, relatively inexpensive, and delivering no radiation, however, the quality of the study is operator-dependent. Transabdominal ultrasonography to detect liver metastases has a sensitivity in the

order of 50%, but when performed with contrast enhancement the sensitivity rate approaches 85% [90]. Due to the inability to assess extrahepatic disease, the utility of ultrasound remains very limited. Ultrasound is most helpful in the intraoperative setting for planning of the resection plane. It is not common to change the pre-operative plan based upon an intraoperative ultrasound (IOUS), but for some patients it provides key information that necessitates changing the operative strategy [91]. In addition, contrast enhanced IOUS can help in identifying lesions as well as assisting with defining the resection margin, especially in patients with multiple colorectal liver metastases or with otherwise isoechoic lesions [92].

Technical Resectability Criteria

The criteria for resectability are defined as follows:

- The ability to attain a negative margin
- Preservation of at least two continuous hepatic segments
- Adequate vascular inflow and outflow
- Adequate biliary drainage and
- The preservation of an adequate future liver remnant volume [93, 94].

Ensuring adequate liver volume has become critically important as insufficient volume has been linked to post-resection liver failure. For patients without any liver disease, a remnant volume of at least 20% results in fewer post-operative complications [95]. For patients who have been treated with chemotherapy, a future remnant liver volume of at least 30% is the recommendation, with some authors advocating for upwards of 40% [96, 97]. This is dependent upon the particular chemotherapeutic regimen and the length of treatment, but it is particularly important for those patients who have developed steatosis or steatohepatitis on surveillance imaging.

Portal vein embolization (PVE) is a technique that can be used to increase the volume of the future liver remnant, which can result in some patients proceeding to resection who previously were not candidates on account of predicted postoperative liver volumes. There have, however, been some disturbing but conflicting reports as to whether PVE may have an effect on tumor progression [98], although a recent trial has demonstrated improved resection rates with no worsening of disease-free or overall survival outcomes with its selective use [99].

Operative Strategy

Pre-operative Preparation

The preparation prior to surgery for colorectal liver metastases is not unlike any other major abdominal surgery. Patients should receive a dose of prophylactic antibiotics within 1 h prior to skin incision and sequential compression devices should

be placed on their lower extremities. Also, depending upon the extent of liver resection that is planned, central venous access can be considered.

Operative Fluid Management and Vascular Control Options

The degree of blood loss is important for any surgery, but may take on a special role for malignancy resection as the number of perioperative blood transfusions for hepatic surgery for colorectal metastases has been linked to overall survival as well as to shortened times until tumor recurrence [100–102].

Intraoperative fluid management and central venous pressure measurement are uniquely managed during liver resections. Studies have shown that with a decreased CVP of <5 mm Hg there is greatly decreased blood loss during hepatic resection as well as a reduction in the amount of transfusions required [103–105].

Additionally, there have been multiple methods described for achieving vascular control during liver surgery. Portal triad clamping (PTC), total hepatic vascular exclusion (THVE) and selective hepatic vascular exclusion (SHVE) have all been well described in the literature, but a clear consensus as to which is best has yet to be determined. The ability to gain vascular control is of paramount importance and all hepatic surgeons should be familiar with these well described maneuvers.

Non-anatomic Versus Anatomic Resection

Ever since Cattell reported the first liver resection for metastatic colorectal cancer in 1943, there have been many advances in the field. For decades, lobar resections were touted as the operation of choice for liver malignancies including colorectal metastases. Over the last 15–20 years, there has been a changing paradigm with regard to this approach. Research groups began investigating the outcomes when hepatic lobe resections were compared with anatomic segmental resections and found that the latter was a feasible approach with no significant difference in survival [106, 107]. As imaging and surgical anatomy became better understood, some surgeons began to attempt wedge resections to further preserve hepatic parenchyma. Many groups have demonstrated that survival and oncologic outcomes are not significantly different when comparing anatomic to non-anatomic resections [108–111]. The primary goal of any surgical resection is to obtain pathologically negative margins, however, there is probably some benefit in preserving as much functioning liver parenchyma as possible, particularly given the risk of liver recurrence which may require repeat surgical intervention. Individuals who have undergone lobar or extended resections may have limited treatment options in the setting of recurrent disease. As long as a pathologically negative margin can be attained, non-anatomic liver resections are a viable option for surgical planning.

Resection Versus Ablation

Ablative techniques such as radiofrequency ablation (RFA), microwave ablation and cryoablation have all been employed to treat a variety of tumors in modern surgical practice. In particular, RFA has been a technique that has been widely used in recent years for patients with colorectal liver metastases. Many studies have found an increased local recurrence rate and decreased overall survival for patients with tumors treated with RFA when compared with those treated with surgical resection [12, 112–114]. However, there have been reports of RFA used for small tumors where the recurrence rates do approach those of surgical resection [115]. Here, patient selection continues to be critical as those lesions >3 cm undergoing ablation tend to have significantly higher recurrence rates.

There has been a recent randomized trial that investigated the efficacy of RFA in conjunction with systemic therapy comparing this with systemic therapy alone for patients with unresectable liver metastases from colorectal cancer. Due to problems with accrual, a difference in overall survival was not able to be detected, but there was a significant increase in progression-free survival for the group that included RFA [116]. Given the difficulty in patient accrual, (downsizing the study to a Phase II trial) it is unlikely that OS will be utilized as an endpoint in the future for any similar study, with PFS acting as a surrogate assessment marker given the nature of responses to liver-directed therapies.

RFA has been most commonly employed in patients who have unresectable tumors, bilateral disease, an inadequate future liver remnant precluding resection, or who are unable to tolerate a major abdominal operation due to medical co-morbidities or performance status. Given the baseline patient characteristics of those who undergo RFA as part of their treatment (compared with those who undergo resection only), there exists an intrinsic selection bias that does make the true efficacy of RFA difficult to interpret since the patients are not strictly comparable [117, 118].

Currently, surgical resection should remain the primary treatment option whenever possible. There is not yet any clearly defined set of criteria for using RFA for colorectal liver metastases, but it may be useful as an adjunct to resection in carefully selected patients with small tumors, or when resection is not possible or refused by the patient.

Synchronous Metastases

Synchronous colorectal liver metastases can be treated in a variety of ways depending upon the individual clinical situation (Fig. 24.3). The two most common sequences are the classic or the staged approach (colorectal then liver resection) and the simultaneous resection. Less commonly performed is the reverse approach where the liver lesions are resected first followed by resection of the colorectal primary.

Staged resections are indicated for situations where complex liver and/or colorectal resections are required in order to achieve negative margins. Additionally, simul-

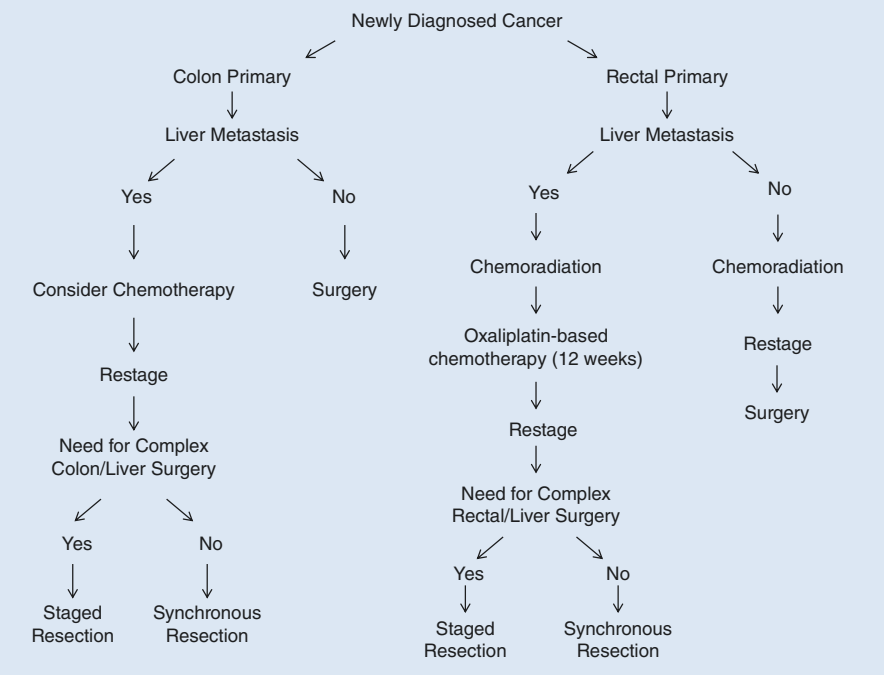

Fig. 24.3 Management schematic for synchronous colorectal liver metastases
There are multiple ways to manage these complicated patients, but here one simplified algorithm is presented. It is critical to note that in the vast majority of cases, complex colon or rectal surgeries should not be combined with major lobar liver resections. These patients should undergo staged resections in order to minimize potential complications

taneous procedures require longer operative times, so that patients with medical co-morbidities which would preclude longer operations are better candidates for a staged approach.

The simultaneous approach is one that has been advocated due to its outcomes with equivalent morbidity and mortality rates, along with a reduced length of hospital stay and decreased costs when colorectal resections are combined with minor liver resections [119–122]. The majority of liver metastases can be treated with segmental or non-anatomic liver resections (Fig. 24.4). In these cases, a minor hepatectomy can be safely combined with most colon and rectal procedures. As the complexity of the intestinal surgery increases, however, so does the potential morbidity of combined resection. While it may be appropriate in selected patients, performing major hepatic resections with simultaneous complex colon or rectal procedures may have a significantly increased risk of perioperative morbidity [123].

All of these patients who present with a rectal primary and synchronous metastases should receive adjuvant therapy although there is no current definitive data for any specific regimen and therapeutic timing. Despite this, it has become increasingly clear that the time interval between chemoradiation and surgery has been

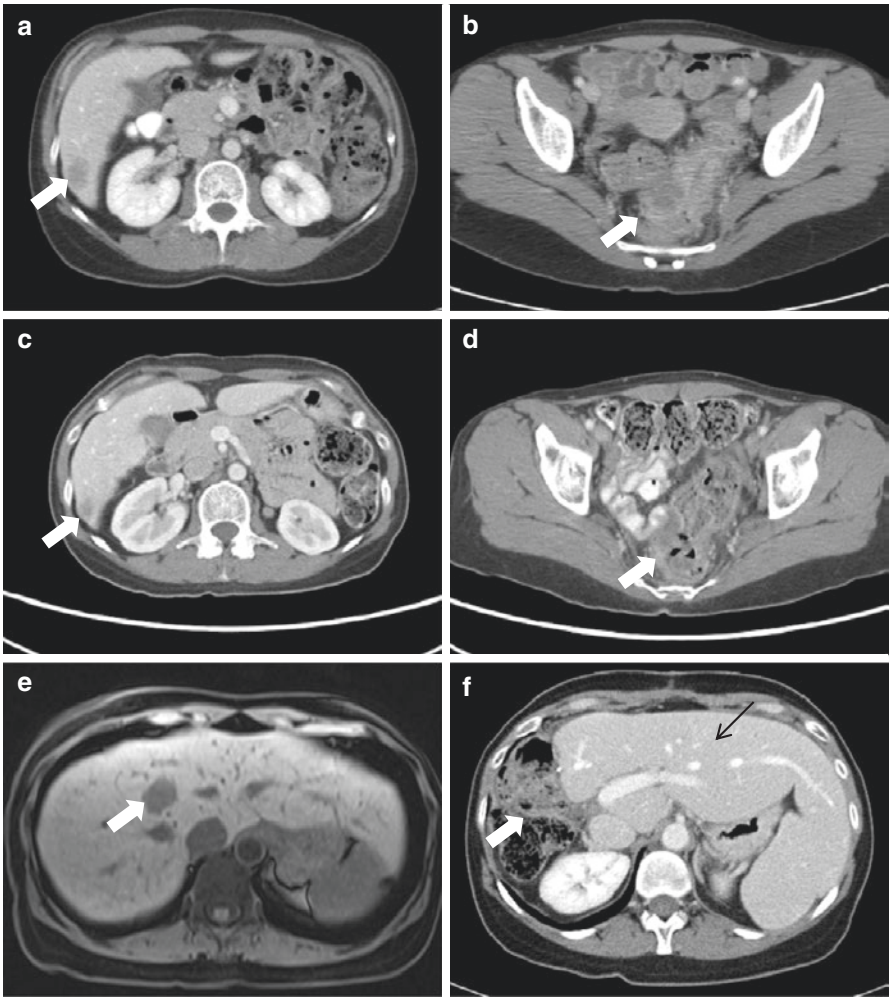

Fig. 24.4 Synchronous liver metastases with a primary rectal cancer
(**a**–**b**) CT scan images from a patient's initial diagnostic imaging. Liver metastasis (a, arrow) in segment 6 of the liver and the primary rectal tumor within the pelvis (b, arrow). (**c**–**d**) CT scan images following 3 months of neoadjuvant chemoradiation demonstrating a response to therapy and a reduction in size of both the liver metastasis (c, arrow) and the primary rectal tumor (d, arrow). (**e**) Approximately 1 year following a simultaneous low anterior resection and segmental liver resection, the patient developed a recurrence in the liver (arrow) as seen on MRI. (**f**) CT scan following right hepatectomy. Post-surgical changes are apparent at the operative site (white arrow), along with compensatory hypertrophy in the left lobe of the liver (black arrow). Notably, there is no evidence of additional disease recurrence in the remaining liver parenchyma

lengthening and may approach 12 weeks. Figure 24.5 shows our approach where patients typically undergo 5 weeks of radiation and chemotherapy following their initial diagnosis. This usually is administered as XELOX (capecitabine plus oxaliplatin)_ with RT although continuous infusional 5-FU is an alternative option.

Whilst patients are recovering from their pelvic irradiation, the plan is to continue with an additional 2–3 cycles of chemotherapy (either as XELOX or FOLFOX) which lasts approximately 6–9 weeks in total. After this, there is a 4–6 week break from all therapies and a restaging with subsequent surgical planning. Here, the decision is made as to whether to proceed with a simultaneous or a staged resection in accordance with the general considerations already mentioned. If a staged procedure is selected, there is usually a 6 week window between the procedures although this period can be lengthened if any complications are encountered after resection of the rectal primary. Once all resections are complete, most patients will continue with adjuvant chemotherapy so that they receive a total of 6 months perioperative chemotherapeutic treatment.

Laparoscopic Liver Surgery

As laparoscopic surgery has become more widespread, it has changed the approach for many different conditions. Laparoscopic liver surgery was first reported in the early 1990s and has been gaining popularity ever since that time. The potential benefits of laparoscopic approaches include smaller incisions, less postoperative pain and a shorter hospital stay on average when compared with open liver surgery. However, this does come with a substantial learning curve [124].

Patient selection is a critical component to successful minimally invasive liver surgery. Lesions that are few in number, those <5 cm in size and lesions located peripherally (segments 2–6) are most appropriate for laparoscopic resection [125, 126]. A recent series analyzed 2804 cases of laparoscopic liver resections for both benign and malignant processes and found that the overall morbidity was 10.5% and the mortality was 0.3% [127]. It is clear that in well-selected patients the morbidity associated with minimally invasive liver surgery is quite low.

While there are no prospective data comparing the short-term outcomes of laparoscopic with open liver resections, there is ample reason to suggest that outcomes for the laparoscopic approach are at least equivalent with open surgery, if not superior. In particular, short-term endpoints such as the intraoperative blood loss and the length of hospital stay are lower with the minimally invasive approach [128, 129].

In the aforementioned series, approximately 50% of patients underwent resection for malignancy and of those patients 35% had colorectal liver metastases [127]. There has been some debate in the literature as to what role minimally invasive surgery should have in cancer surgery and if the oncologic outcomes are equivalent to those of open surgery. A study conducted in two French centers specializing in hepatic surgery suggests that the oncologic outcomes are comparable between open and laparoscopic surgery specifically for colorectal metastases [130]. Here, 60 patients were included in each group and were matched according to preoperative prognostic variables. Overall survival was 64% in the laparoscopic group and was 56% in the open group (P = 0.32). Similarly, a multicenter series analyzing 109 patients who underwent laparoscopic liver surgery (both major and minor hepatectomies) reported a 5-year overall survival of 50% [131].

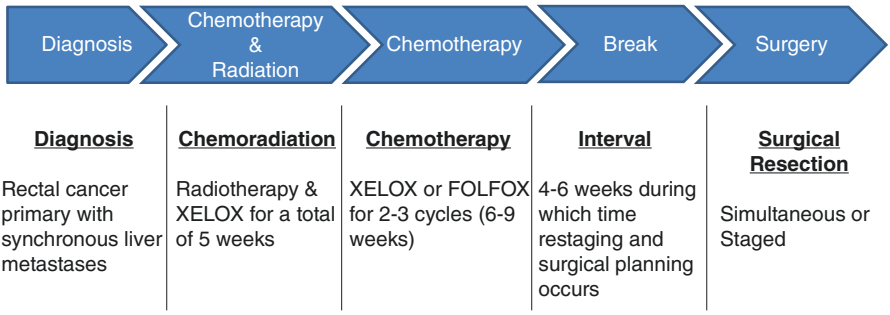

Fig. 24.5 Timeline for the treatment of rectal cancer with synchronous liver metastases
After the diagnosis of rectal cancer with synchronous liver metastases, patients undergo 5 weeks of radiation and chemotherapy. While recovering from radiation, patients continue to receive additional chemotherapy (2–3 cycles) for the next 6–9 weeks. Following this there is a break for 4–6 weeks whilst restaging is conducted and then subsequent surgical planning

Multiple series have reported equivalent oncologic outcomes between open and laparoscopic surgery, but it must be emphasized that patient selection plays a key role in achieving such results and must be given the utmost consideration in preoperative planning.

Perioperative Morbidity and Mortality

Surgical resection for colorectal liver metastases remains the cornerstone of treatment for this disease process. As patient selection, surgical techniques and perioperative care have improved in recent decades, the mortality rates have also improved and have even been reported as less than 1% overall at large-volume referral centers. Table 24.3 lists the mortality and morbidity rates of select series [13–15, 47–52, 58]. Despite all of the aforementioned improvements, perioperative hemorrhage and liver failure continue to be responsible for the majority of the mortalities following liver resection for colorectal metastases.

The morbidity associated with liver resection remains quite high, with many series reporting at least 20% of their patients having some type of complication. It is important to note that the risk of complications increases steadily along with the number of resected liver segments, where lobar or extended resections have the greatest attendant morbidity [49, 132].

In terms of liver-specific complications, post-operative liver failure occurs in approximately 4–11%, biliary fistulas in 3–4% and perihepatic abscesses in between 2% and 6% of cases [49, 50, 133, 134]. While it is one of the most worrisome complications during and following liver surgery, perioperative hemorrhage is rare and only occurs in approximately 1–3% of patients [50, 132, 133].

Table 24.3 Postoperative morbidity and mortality after resection of colorectal liver metastases

Author	Year	Number of patients	Morbidity (%)	Mortality (%)
Scheele	1995	434	22	4.4
Nordlinger	1996	1568	23	2.3
Fong	1999	1001	31	2.8
Minagawa	2000	235	–	0
Choti	2002	226	18.6	0.9
Pawlik	2005	557	–	0.9
Tomlinson	2007	612	–	5.2
House	2010	1037 (era 1: 85–98)	44	2
		563 (era 2: 99–04)	44	0.5
Vigano	2013	323	28.5	0.5
Gur	2013	157	24	1.26

With the use of upper abdominal incisions and the proximity of the liver to the diaphragm, it is not surprising that approximately 20% of patients develop some type of pulmonary complication including symptomatic pleural effusions (9%), pneumonia (3%) and pulmonary emboli (1%) [132]. Cardiac complications occur in 9% of patients with the vast majority being arrhythmias [132].

Recurrent Lesions and Patterns of Recurrence

Liver resection is the standard of care for colorectal metastases, however, the majority of patients will experience a disease recurrence following their initial surgery. Overall, it has been reported that approximately 50–70% of patients will recur following their initial surgery [134]. The liver will be the sole site of recurrence in approximately 30–40% of these patients [135], stressing the importance of liver-preserving surgical techniques.

In a Johns Hopkins study by de Jong et al. [134] of 1669 patients of whom 947 developed a recurrence following resection and/or RFA, the distribution between intrahepatic and extrahepatic disease sites is similar when accounting for both initial and late recurrences. Approximately 39% of patients developed a liver-only recurrence, 34% had evidence of disease only at an extrahepatic site and 27% had both intra and extrahepatic sites of disease. Other studies have demonstrated extrahepatic sites to be the slightly more predominant [136, 137].

For those patients who do have a recurrence after a primary liver resection for colorectal metastases, the median time to recurrence has been shown to range from approximately 14–16 months with many of these patients being re-operated on within 1 year of their initial liver surgery [134, 136, 138].

Predictors of shorter recurrence-free survival include: a rectal primary tumor site, primary tumor lymph node metastases, synchronous presentation, a prior history of RFA treatment and a disease-free interval <12 months [134].

There has been a growing body of literature to support repeat resections of colorectal liver metastases and as the criteria for resection expands more patients are able to undergo repeat surgery. The outcomes of repeat resection have been quite good and can in some series approach those of patients who have only had a primary liver resection. There is some variation in the reported short-term morbidity and mortality rates, but many studies have demonstrated equivalent or only slightly worse rates when compared with primary resections. Morbidity reports have ranged from approximately 7% to 34% [139, 140] with one smaller series from Vanderbilt University in Tennessee, noting complication rates of 60% [141]. Additionally, long-term outcomes reporting the 5-year survival rates following repeat liver resections have ranged from approximately 30% to 50% [138, 140, 142, 143], but recent reports have noted survival rates of over 70% [144, 145].

It is clear that repeat liver resections for recurrent colorectal liver metastases are associated with acceptably low morbidity and mortality rates in both short- and long-term follow-up after surgery. These operations will continue to be performed where appropriate patient selection with a multi-disciplinary approach remains critical to continued successful outcomes. In a Tokyo study by Saiura et al. [144] given the similar indications for repeat surgery as for the primary metastasectomy, nearly half of the recurrences after initial liver resection were salvaged by repeat liver surgery. Similar favorable outcomes were demonstrated by this group beyond the liver-only cases to the lung-only patients.

Rectal Cancer Specifics

While the body of data surrounding colorectal liver metastases has increased, much of the work has not made any differentiation as to whether the primary lesion was in the colon or the rectum. It is notable that some studies have analyzed the primary site as a potential prognostic factor for overall survival in patients treated for liver metastases and in this regard, the vast majority have found no significant difference between colon and rectum primaries [15, 47, 48, 50].

Importantly, the patterns of recurrence have been shown to be somewhat different. It is still true that many patients will have disease recurrences in the liver. However, for patients who have been treated for liver metastases secondary to rectal cancer, there is an increased rate of local recurrence in the pelvis [146]. Conversely, of those patients with pelvic recurrence, over half also developed liver recurrence although both DFS and OS were similar in patients undergoing hepatic resection regardless of whether the primary was colonic or rectal. Additionally, especially for lower rectal cancer lesions, there appears to be an increased rate of extrahepatic recurrence, which is often located in the lungs [147].

Historically, there has been some reluctance to combine colorectal and liver resections within the same procedure. As mentioned earlier, with improvements in surgical techniques and perioperative care, these combined procedures are becoming more commonplace. There is not much data looking specifically at combined

rectal and liver resections, but a recent report by Silberhumer et al. demonstrates that in carefully selected patients, even major liver resections can be combined with rectal cancer operations and are able to achieve acceptable morbidity rates [148]. Within this study, there was bias however, since most of the patients requiring an abdominoperineal resection or who had large or numerous liver lesions were preferentially treated with the staged approach. The safety of the combined procedures and the acceptable outcomes are predicated upon careful and rigorous patient selection, which cannot be over emphasized. As with conventional Stage IV cases after resection of the primary and a metastasectomy (either staged or synchronous), it is intuitive that adjuvant chemotherapy should be continued, although it is unclear for how long and of its overall survival benefit. The specific benefit for rectal cancer patients in particular also remains unproven [60, 148–150]. The data are biased with reflection of a trend over time towards more hepatic parenchyma sparing surgeries and a greater use of adjuvant chemotherapy in the synchronous cases [151]. If simultaneous surgery is used, it has been suggested that the 'clean' liver procedure should be performed first where during the hepatectomy, low fluid administration is used to prevent venous bleeding from the cut hepatic resection surface and permitting fluid 'resuscitation' during the rectal procedure [146, 152, 153].

Disappearing Liver Metastases

With the increasing use of neoadjuvant chemotherapy, previously visible liver metastases recognized on cross sectional imaging will often disappear on subsequent scans. Disappearing liver metastases (DLM) present treatment challenges for multidisciplinary teams, particularly when the lesions are outside of the planned resection area. Multiple groups have reported the incidence of DLMs which have ranged from 6% to 37% [154–158]. It is likely that the use of different imaging modalities as well as different chemotherapy regimens contribute to this wide-ranging incidence. Moreover, the duration of administration of neoadjuvant therapy (more cycles) and the size of the initial lesions (smaller metastases) will contribute to the variability in the reported DLM incidence during therapy.

The multidisciplinary team must closely monitor patients with colorectal liver metastases as they undergo pre-operative chemotherapy in order to ensure the optimum timing of surgery and to monitor potential problems of the primary (most notably obstruction) and obviate the need for urgent surgeries which can seriously compromise morbidity and perioperative mortality. Regarding colorectal liver metastases, as previously discussed, MRI is the best modality for pre-operative characterization, especially in the setting of neoadjuvant chemotherapy [159]. In particular, patients who have developed steatosis on account of their chemotherapy regimen are at an increased risk of being inadequately evaluated by CT scans [160]. A study by Benoist et al. noted that over 25% of liver lesions that disappeared on pre-operative imaging were able to be identified at the time of exploration [155].

If there is concern about potentially disappearing lesions that may be missed at the time of surgery, coils have been used as markers to guide planning [161] with placement behind the deep margin of lesions under CT or US guidance. Small coils are specifically used so as not to impede the peripheral blood flow of the lesion or the chemotherapy distribution. The benefit may be seen in deep-seated rather than capsular lesions and in patients with attendant post-chemotherapy steatosis (particularly post 5FU or post-irinotecan). Given that a complete radiologic response does not equate to a complete eradication of all disease, a recent consensus statement recommended that all original disease sites should be resected when able [93]. Another approach would be to resect the visible disease sites and treat the DLMs should they recur in the future. An additional option is to limit the neoadjuvant chemotherapy to a short course so that all tumors can be resected prior to any disappearances. Further investigation will be needed to determine whether any of these approaches will ultimately lead to higher overall survival rates, but it is quite likely that any of the above will be acceptable in properly selected patients.

A concern with DLMs is that the complete radiologic response is not necessarily predictive of a complete pathological response, which in some studies has been associated with an improved survival rate [162]. The reported rates of complete pathologic response range from approximately 20% to 45% [154, 155, 163]. Also, for untreated DLMs, there is an increased local recurrence rate when compared with resected DLMs, however, it is notable that there may not be a survival disadvantage in these patients despite their local recurrences [158]. Individuals who do recur should be offered a repeat resection if they meet the appropriate criteria. Although a complete pathological response is relatively uncommon in colorectal metastatic disease, an objective response is frequent and more likely to be noted in younger patients (<60 years of age), those with smaller hepatic metastases (<3 cm in diameter) and those with initially lower CEA levels [162]. These patients are more likely to demonstrate improvements in their disease-free survival where a prospective trial comparing neoadjuvant therapy with adjuvant therapy after liver resection will determine the optimal perisurgical treatment regimen [164].

Conclusion

The care of patients with colorectal liver metastases has changed markedly over recent decades. Improved imaging, chemotherapeutics, patient selection, perioperative care and surgical techniques have allowed patients once deemed to have unresectable disease to proceed to surgery. Overall outcomes and survival have improved, with the mortality rates being less than 1% at major referral centers. As increasingly larger and more numerous tumors are being successfully resected in a single operation, patient selection will become even more important underscoring the need for multidisciplinary care of these patients so as to ensure optimal surgical planning.

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Chapter 25
Managing Non-Hepatic Metastatic Sites: Lung and CNS

Ishwaria Subbiah, Cathy Eng, and Emil Lou

This chapter presents data pertaining specifically to pulmonary and CNS-related metastases from colorectal carcinoma. Most studies on these unusual sites of metastatic disease do not differentiate between rectal and colonic cancers. The data would suggest in small series that selected surgical resection in combination with adjuvant chemoradiation may lead to improved survival in these settings. There are prognostic factors which are associated with a better outcome based upon the locale of the tumor, the performance status, a longer disease-free interval and control of the primary without extrametastatic disease.

Approach to Oligometastatic Disease in the Lung

Patients who undergo resection of primary colorectal cancer (CRC) with or without adjuvant chemotherapy have had therapy with curative intent. However, when a subset of these patients does recur, examination of the incidence and sites of recurrence advances our understanding of the patterns of failure and aids in the design of future studies designed to overcome these disease characteristics leading to treatment failure. In this regard, one European study analyzed 2567 CRC patients who

I. Subbiah
Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

C. Eng
Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

E. Lou (✉)
Department of Medicine, Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA
e-mail: emil-lou@umn.edu

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had a resection with curative intent from the cancer registry of the Côte-d'Or (France) [1]. This study demonstrated a 5-year cumulative rate of local recurrence to be 12.8%, while the rate of distant metastases was higher at 25.6%. The rates of local recurrence showed a predictable concordance with the increasing stage of colon cancer at diagnosis, with stage I cancers having the lowest rate of local recurrence (4.9%), stage II with 11% and stage III with 23.5% ($P < 0.001$). Similar distribution was noted in the rates of distant metastases which reached as high as 48% in stage III patients whilst remaining at 6.4% in stage I disease.

An in-depth examination of the patterns of failure suggests that tumor location was significantly associated with increased local recurrence, where rectosigmoid junction tumors locally recurred more often than tumors within the right or left colon ($P < 0{\cdot}001$). Site of metastatic recurrence favored the liver (43.5% of distant recurrence), peritoneum (14.6%) and the lung (10.2%) with less than 2% involving the brain and bone. Furthermore, a separate analysis of data on metachronous lung metastases from CRC highlighted the role for resection of oligometastatic pulmonary disease where the 3-year relative survival of 13.8% for metachronous lung metastases improved to 59.2% after a resection with curative intent, an improvement that is echoed in similar analysis of CRC patients [2–4].

Patient Selection for Metastasectomy

The optimal patient selection for curative pulmonary metastasectomy remains controversial with numerous retrospective evaluations of patients undergoing resection of oligometastatic CRC pulmonary lesions. Few studies however, stratify their results based upon the site of the primary lesion (rectal *vs.* colon) limiting interpretation as it applies specifically to rectal cancer. Since the incidence of pulmonary metastases is comparable, however, in both colon and rectal cancer, the current management approach is shared for all CRC primary sites. Studies to date have identified a myriad of patient and disease characteristics that, on multivariate analysis, have emerged as predictors of survival and recurrence (Table 25.1). Relevant prognostic factors which consistently recur throughout several studies include the number of pulmonary metastases, the presence of an elevated level of prethoracotomy carcinoembryonic antigen (CEA, >5–10 ng/ml), the completeness of resection (evidence of residual disease) and lymph node involvement [5–10]. The 5-year survival of patients who underwent an isolated (single) metastasectomy compared with those undergoing a multiple metastasectomy was 43.6% and 34%, respectively [6]. This same study also demonstrated that patients with a normal preoperative CEA level had a significantly and strikingly greater 5-year survival than those who had an elevated CEA (58.2% vs 0%, $P = 0.0001$). The extent of lymph node involvement was prognostic for the 5-year survival where patients with intrapulmonary nodal involvement had a median survival of 86 months whilst those with hilar (and 6 patients with mediastinal) lymph node metastases had a median survival of 24.5 and 34.7 months, respectively. Overall, the intrapulmonary group had a

Table 25.1 Predictors of recurrence and survival in patients undergoing resection of CRC pulmonary metastases

		# of studies identifying each characteristic	
Characteristic	*n*	Survival	Recurrence
Higher number of pulmonary metastases	39–378	8	1
Pre-thoracotomy CEA (>5–10 ng/mL)	39–139	7	
Completeness of resection	86–170	3	
Lymph node involvement	39–165	3	
Short disease-free interval	61–378	2	1
Single versus bilateral metastases	84–128	2	1
Wedge versus anatomic resection	75, 153	2	
Extrapulmonary metastasectomy	125, 159	1	1
Largest size of pulmonary metastases	75	1	
Stage of the primary tumor	128	1	
Time to pulmonary recurrence	125	1	
Age (<65 years) of patient	378		1
Female sex	378		1
Simultaneous versus staged resection	165	1	
Tumor load	110	1	
Intraoperative blood transfusion	153	1	

Adapted from Blackmon et al. [14]
n denotes the number of patients included in studies which evaluated the characteristic

5-year survival of 78.5% and the hilar/mediastinal group had a 5-year survival of 0% (P = 0.008/P = 0.07) [9]. A long disease-free interval (DFI) from the diagnosis of the primary CRC to the development of lung metastases, as well as the presence of unilateral versus bilateral pulmonary metastases, have also emerged as important predictors not only of disease recurrence but also of overall survival [11–13]. A DFI of ≥36 months has been identified as a reliable predictor of overall survival [8].

In a large series of 229 patients reported by Blackmon et al. [14] from our institution, the presence of >3 lung metastases at the time of the first metastasectomy (HR, 1.19; 95% CI, 1.071–1.321; P = 0.001) and a pre-operative DFI <3 years (HR, 0.99; 95% CI, 0.973–0.997; P = 0.013) both significantly predicted for regional recurrence within the lung. Based upon these data, the identification of patterns of recurrence through the characteristics of the tumor may facilitate the decision concerning the appropriate adjuvant procedures directed towards mitigating local or regional recurrence.

Preoperative Chemotherapy Prior to Pulmonary Metastasectomy

Preoperative predictors of prognosis may identify subsets of patients who can benefit from a multimodal therapeutic strategy incorporating preoperative chemotherapy prior to a potentially curative resection of oligometastatic disease. The actual

benefit of preoperative chemotherapy prior to pulmonary metastasectomy, as well as the optimal regimen, remains to be delineated. One retrospective study from our institution investigated the preoperative treatment regimens (if given) and outcomes of patients with resected primary tumors who then underwent pulmonary metastasectomy [15]. This study attempted to identify patient and tumor characteristics that may have prompted the clinician to consider preoperative chemotherapy prior to pulmonary metastasectomy. The patient groups are not strictly comparable as specifically, those patients in the preoperative chemotherapy arm were more likely to have a stage IV CRC at the time of diagnosis ($P = 0.015$) and had more than two pulmonary lesions at the time of metastasectomy ($P < 0.001$). The size of the largest lung mass was also greater in the pre-operative chemotherapy arm (1.8 cm *vs.* 1.3 in the surgery alone arm, $P = 0.009$). Of the 115 patients in the surgery alone arm, 44 patients (38%) received chemotherapy (oxaliplatin, irinotecan, capecitabine, or other) post-operatively after pulmonary metastasectomy, of whom 38 were treated without evidence of disease to reduce the risk for disease recurrence. The median time from their surgery to the initiation of chemotherapy was 1.5 months. There was a remaining six patients who showed evidence of active disease at the time of their first post-operative imaging. Of these cases, four had developed new pulmonary lesions, one a new liver metastasis and one new intra-abdominal lymphadenopathy with a rising CEA level. By comparison, in the pre-operative chemotherapy arm, of the 114 patients who received preoperative chemotherapy prior to pulmonary metastasectomy, 54 (49%) received adjuvant chemotherapy or radiation with 37 (32%) having no evidence of active disease and with 17 patients demonstrating new lesions in the lung and liver or with positive surgical resection margins.

These preliminary findings have prompted a prospective study currently under design so as to identify those patients with pre-treatment characteristics predictive of post-treatment disease recurrence. These patients will then be randomized to receive pre-operative chemotherapy (investigator's choice) or proceed directly to pulmonary metastasectomy. This Phase III trial is the first to randomize patients with a prior CRC resection to a process of active monitoring with pulmonary metastasectomy where the primary end-points will include overall survival, relapse-free survival and quality of life. Future prospective studies employing a multimodality treatment approach both pre- and/or post-operatively are underway.

Molecular Markers of CRC Metastasis to the Lung

In the era of molecular analysis and genomic profiling, there are more data identifying molecular features of rectal tumors that increase this metastatic risk. The most prominent candidate is RAS. Here, there are multiple forms of the RAS gene reported to occur at similar rates amongst colon and rectal cancers where KRAS is mutated in 35–40% of colorectal cancers and NRAS is mutated in an additional 3–5% [16–18]. The testing of multiple forms of RAS (sometimes referred to as "All-RAS testing") became established in 2014 and has evolved to a new

standard-of-care in CRC molecular testing [17]. Mutations in KRAS and NRAS are mutually exclusive as are RAS and BRAF mutations where currently BRAF is not considered a predictive biomarker although it may potentially be a negative prognostic biomarker [17, 19, 20].

Even though CRC metastasis to the lungs are potentially treated with resection and chemotherapy in cases of limited, resectable disease, the identification of molecular markers which predict for metastasis risk would improve the clinical surveillance approaches and possibly impact post-treatment prognosis. The assessment of RAS status and its correlation with pulmonary metastasis has been investigated in several studies. Yaeger et al. [21] examined tumors and outcomes from 1095 patients with metastatic CRC treated at Memorial Sloan-Kettering Cancer Center, with an available dataset of tumor genomic profiles that included assessment of RAS genotyping. In this study, lung metastases were significantly more prevalent and lung was the first metastatic site in patients with RAS mutations (22% in RAS mutant tumors, 13% in wild-type; $P < 0.01$). The cumulative incidence over 2 years for subsequent site-specific metastasis after a diagnosis of metastatic disease had been made was even higher for lung (32.5% for RAS mutants *vs.* 19% for wild-type; $P = 0.001$) with a higher cumulative incidence also noted for bone (8.8% *vs.* 4.4%, respectively $P = 0.024$) and for brain (1.4% *vs.* 0.2%; $P < 0.01$). The hazard ratio for likelihood of lung metastasis was 1.52 in favor of RAS mutant tumors ($P < 0.01$). There was a general trend toward higher numbers and faster development of distant metastases to the lungs, bone and brain potentially providing insight into the overall reasons for a generally worse prognosis in this population. The suggestion here is also that RAS mutations are implicated not only in tumor initiation but also in tumor progression. In another smaller but similar study, Tie et al. [22] examined 50 cases of matched primary CRC tumor in patients with lung metastases. The prevalence of KRAS mutation in this study was high (62.0%) with a high concordance rate of metastatic tumors compared with the primary tumors. In this study 35.1% of patients had rectal primary malignancies (55.4% colon primary, 9.5% not specified). Compared with independent primary cancers, KRAS mutations were more common in both lung and brain metastases and KRAS status was associated with lung relapse (HR = 2.1 95% CI 1.2–3.5; $P = 0.007$) and not liver relapse.

A similar single-institution study by Schweiger et al. [23] examined the outcomes from 44 patients following pulmonary metastasectomy in those cases with primary CRC. Overall, 48% of tested primary tumors harbored some form of KRAS mutation. None contained a BRAF mutation and 49% contained expression of epidermal growth factor receptor (EGFR). The correlation of KRAS status to outcome determined that the presence of a KRAS mutation in the primary tumor led to significantly less time to lung-specific recurrence following resection of a pulmonary metastasis, as well as a higher number of metastatic lesions to the lung overall. KRAS mutations were present in 46% of resected lung metastases and nearly all of these (89%) were located in codon 12. Of the 44 patients, 21 (58.3%) had tumors originating in the rectum. The percentages of KRAS mutations *vs.* wild-type differed significantly depending upon the location of the tumor (namely left- or right-sided colon compared with rectum) such that 71.4% of the rectal tumors were

KRAS wild-type compared with 5/11 (45.5%) wild-type RAS for left-sided colonic tumors. As with most molecular studies in this field, testing is broadly applied to colorectal cancers as a single category, but future studies may consider stratifying these tumors according to their locale with further rectum-specific data. One study from Lyon by Derbel et al. [24] examining the molecular profiles of rectal carcinomas specifically detected generally lower rates of mutations in KRAS (23.5%), BRAF (2%), and PIK3CA (4%) than has been reported for colon cancers. Although the numbers were small, no patient with a local recurrence of their rectal cancer had a RAS mutation.

KRAS is currently used as a predictive biomarker in order to stratify patients eligible for and likely to benefit from EGFR-targeted immunotherapy (cetuximab or panitumumab) [19]. Modern standard-of-care does not apply RAS testing results presently for use in follow-up surveillance and current guidelines do not take into account or discriminate between patients with RAS-mutated or wild-type tumors. Concerning this point, a retrospective analysis of patients with stage III colon cancer receiving FOLFOX with or without cetuximab (the PETACC8 phase III trial) showed that in general, patients with KRAS mutations had a shorter time to recurrence [25] and in subset analysis confirmed that the population in which this was highest was in patients with KRAS mutations in codon 12. These cases had more distal rather than proximal tumors. The above studies demonstrate that KRAS may potentially prove to be an effective prognostic biomarker where KRAS exon two mutations are independent predictors for shorter recurrences in more advanced distal tumors. If these findings are confirmed, they may have potential value by altering surveillance guidelines to include more frequent radiologic surveillance designed to detect distant metastatic disease in patients with RAS-mutated primary tumors.

Molecular Markers and Management of CRC Metastases to the Brain/Central Nervous System (CNS)

Gastrointestinal cancers in general do not commonly metastasize to the brain. The rate of metastasis of colorectal cancers to the central nervous system is between approximately 1–5% [26–31]. Most such metastases are solitary rather than multiple [19, 32]. An overwhelming number of CRC patients with brain metastases (nearly 80%) will first have developed metastases to the lung [16] and as noted earlier in this chapter, few studies differentiate between or stratify outcomes for rectal cancer specifically, so that this short review is being extrapolated from non-discriminatory CRC data.

Yaeger et al. [21] in a paper already discussed for pulmonary metastases examined the effect of RAS mutations on the prevalence and the risk of metastatic spread to the brain. The presence of a RAS mutation (in KRAS exons 2, 3, or 4, or in NRAS) was generally associated with a higher rate of brain metastasis, although the difference was not statistically significant. In this study, the brain was the site of first metastasis for 0.5% of CRC patients with mutant RAS, compared with 0.2% with

wild-type RAS status (P = 0.61). The cumulative risk of metastasis to the brain within 2 years after diagnosis was significant for patients with mutant RAS (1.4% *vs* 0.2%, P < 0.01). When controlled for other factors, RAS was an independent predictor of CRC brain metastasis using univariate (HR 3.3, P < 0.01) or multivariate (HR 3.7, P < 0.01) analysis. With follow-up over a long duration of this overall population with metastatic CRC, of those patients who developed brain metastases over 8 years, there was a significantly higher overall incidence of brain metastases in those patients with any RAS mutation (n = 28) compared with the RAS wild-type (n = 9; P < 0.01). Of all forms of RAS mutations, although the numbers were comparatively small, the G12D variant was most prominent in this population. Equally, PIK3CA is an interesting potential biomarker as the gene encodes a subunit of the heterodimer phosphatidylinositol 3-kinase (PI3K) lipid kinase which regulates cell growth and survival. These investigators also examined PIK3CA mutation status in this same patient population and detected this form of mutation in 7 of 25 patients with CRC brain metastasis over an 8-year follow-up period. The overall prevalence of a higher incidence of brain metastasis in the RAS-mutated CRC population is one potential explanation why patients with this mutation tend to have a worse prognosis, although the overall prevalence remains low in this tumor type. In a separate Australian study of 100 CRC cases by Tie et al. [22] with matched primary and metastatic tumors, the prevalence of KRAS mutations in brain metastases was 56.5% and was generally higher in those with both brain metastases and lung metastases (62.0%) as opposed to those with liver metastases (32.3%). In this study, there was a high concordance between primary and metastatic sites of RAS expression.

Diagnosis and Management of CRC Metastasis to the CNS

The overall survival of patients with CRC who develop brain metastasis is relatively poor, with a median survival of 4.2 months reported by Zimm et al. in the early 1980s [26]. More recent retrospective studies from Korea [33] and Japan [34] have also reported median survivals of only 5.0 and 5.4 months, respectively where in an analysis by Suzuki et al. [34] patients with rectal primaries had a longer median overall survival (6.7 months) when compared with those with colonic primaries (5.0 months), although this difference was not statistically significant (P = 0.52). Nonetheless, these numbers stand in stark contrast to the median survival range of 21–24 months for patients with metastatic CRC in general. In this respect, a recent retrospective analysis of 228 patients from the Munich Cancer Registry [35] reported the development of brain metastasis at a median time of 29.2 months from the diagnosis of CRC. Patients were predominantly male (59%) with a median age of 63 years. Ninety-three of these 228 patients (42%) had rectal tumors as the primary site of CRC malignancy.

The management of CRC metastases to the CNS (comprising the brain parenchyma and spinal cord and including leptomeningeal metastasis) is essentially the same as brain metastases originating from other systemic sites. For over two decades, the standard-of-care for solid tumor brain metastases in general has encom-

passed maximally safe surgical resection followed by radiation to decrease the risk of recurrence [36]. This combination is preferred compared with radiation alone, with a median survival reported to be as long as 15.2 months for CRC patients able to undergo neurosurgical resection with curative intent. In the comparative study by Suzuki et al. [34] 46 of 113 CRC patients with brain metastasis were able to undergo curative neurosurgical resection and of these, 22 (48%) had rectal primaries, with a median overall survival of 13.3 months. This outcome compared with 24 (52%) with colonic primary tumors which did not reach statistical significance (P = 0.78). There are general concerns that CRC brain metastases are relatively radio-resistant, however, there have been no sufficiently powered scaled studies which currently address this question [37]. An improvement in response in such relatively radio-resistant cases may be seen with whole brain irradiation (WBI) doses exceeding 30 Gy and in those patients with a better overall performance status, fewer (or isolated) brain metastases and a lack of coincident extracerebral metastasis [38, 39].

As CNS metastasis is relatively uncommon in CRC, assessment is not a common part of the standard-of-care staging for colorectal cancer in the absence of neurologic functional changes and/or changes in mental status which warrant further evaluation. When warranted based upon the occurrence of these symptoms, magnetic resonance imaging (MRI) of the brain, rather than computed tomography (CT), is the preferred method of radiologic evaluation [32, 40]. Once a mass is detected on imaging, referral to a specialty neurosurgeon with experience in intracranial tumors is warranted for assessment of potential safe resection. Whereas metastatic tumors arising from renal cell carcinoma or melanoma, for example, are prone to inducing intracranial hemorrhage, this has not been found to be the case commonly with tumors derived from CRC. There has been an ongoing debate regarding the best practice management of single or multiple brain metastases arising from systemic malignancies. Such issues include the use of surgical resection versus stereotactic radiosurgery, whether to add whole-brain radiation (WBI) to stereotactic radiosurgery or vice versa, or to only use one modality in combination with systemic therapies. This issue will be further assisted by adequate stratification of patients based upon known risk factors. In this regard, an EORTC study examining whole-brain radiation therapy (WBRT) following stereotactic radiosurgery or resection of 1–3 brain metastases from patients with solid tumors and stable systemic disease, demonstrated that the addition of WBRT led to decreased intracranial relapse but did not impact overall survival [41]. In this Cologne study 8% of the patients had a colorectal primary malignancy, however, the study did not stratify the results based upon tumor type.

Stratification of CNS Metastasis to Predict Prognosis

Clinical factors such as age (<65 years), Karnofsky Performance Status (KPS) (≥70), the extent of control of the primary site of malignancy and absence or extent of extracranial metastasis are factors comprising the Recursive Partitioning Analysis

(RPA) Classification scores that help determine overall prognosis in the brain metastasis population [39, 42] There is no specific RPA or assessment score particular to CRC malignancy, but these approaches are broadly applicable to systemic CNS metastasis in general and there has been investigation into estimating the survival based upon the primary site of malignancy which includes gastrointestinal malignancies in general [28]. Sperduto et al. [43] from Minneapolis have proposed a Graded Prognostic Assessment (GPA) of brain metastases in various forms of solid tumor malignancies. The GPA varied depending upon the tumor type and included an assessment of factors including the Karnofsky Performance Score, the age and the histologic subtypes of the specific cancers (e.g. in breast carcinoma). In this study, gastrointestinal (GI) cancers were grouped together and not stratified by tumor site or location with the GPA for GI cancers using the KPS to calculate the total GPA score as a potential predictor of median overall survival and the risk of death. A subsequently reported RTOG study (9508) examining WBRT with or without stereotactic radiosurgery (SRS) in solid tumor patients with 1–3 brain metastases has included the GPA score for patients stratification [44]. While in general there was no benefit to the addition of SRS as a whole, patients with the highest GPA did have a survival advantage with addition of SRS to WBRT, regardless of the number of brain metastases. Most patients in this cohort had lung cancer with 4.5% having GI cancers in general, although the results were not stratified by primary tumor type.

In a retrospective analysis of 39 Korean patients with CRC and brain metastases, Kye et al. reported several poor prognostic features including uncontrolled extracranial brain metastases, multiple brain lesions, bilateral brain metastases and serum levels of CEA greater than 5 ng/ml [33]. Aggressive surgical resection was determined to be the only significant factor improving the median overall survival in this population, even in patients with more than one metastasis. The role of surgical resection in improving survival has been further supported by other studies identifying two or fewer brain metastases, an absence of extracranial metastasis and no emergence of secondary brain metastatic lesions as favorable independent prognostic features in this population [34] with in this study by Suzuki et al. the rectum as the site of the primary lesion in 43% of reported patients.

Palliation of Patients with CRC Metastasis to the CNS

In addition to cancer-directed approaches as outlined, palliative measures are equally if not more important for the management of CNS metastasis-related symptoms. Several examples include the use of corticosteroids and antiepileptic medications as needed in order to alleviate peri-tumoral edema which may vary depending upon the location of the metastasis within the brain parenchyma [45]. A team approach to the care of CRC patients who develop CNS spread of malignancy is essential and will likely include multidisciplinary consultation and input from neurosurgeons, radiation oncologists, neurologists, neuro-oncologists and medical

oncologists with expertise in the management of patients with brain metastases and CRC. Regarding the use of systemic agents for the treatment of extracranial metastatic disease, consideration must be given to proper wound healing in cases of surgical resection of CNS metastasis. This is particularly critical when including bevacizumab, the monoclonal antibody targeting vascular endothelial growth factor (VEGF) and which is FDA-approved for use in combination with 5-fluorouracil (5-FU)-based chemotherapy treatment for metastatic CRC. Following the paradigm established for solid tumors, mostly lung cancer, bevacizumab has been shown to be potentially safe and effective for the treatment of both systemic and intracranial metastases following resection or stereotactic radiosurgery treatment [46].

It is possible that the risk of intracranial hemorrhage in treated brain metastatic lesions may vary based upon histologic subtypes of CRC and certainly may differ from other common metastatic tumor types (e.g. lung adenocarcinoma, renal cell carcinoma). The risks of using bevacizumab (including the risk of intracranial hemorrhage) for unresectable intact brain metastases have not been elucidated for rectal or colon cancers specifically. Information concerning the safety of use of bevacizumab for brain metastasis in CRC specifically is limited to isolated case reports [47–49]. In terms of the choice of chemotherapy agents, there are no agents which are currently specifically recommended for CRC patients with CNS metastases where oncologists typically choose those combination regimens which are the standard-of-care for systemic metastasis in general.

Bevacizumab is also FDA-approved for recurrent glioblastoma (malignant primary brain tumors) and is known to alleviate tumor-related swelling in that tumor type as well. The use of this agent may spare patients from corticosteroids to treat related symptoms and thus spare them from common side effects including insomnia, hyperglycemia and anxiety. In general, in the era of biologic therapies and the more effective use of combination chemotherapies resulting in prolonged survival of patients with metastatic colorectal cancers, a rise in the incidence of CNS metastases due to disease prolongation may be anticipated [50]. An example of a cerebellar metastasis and case study is shown in Fig. 25.1.

Conclusions

The management of rectal cancer metastasis specifically to the lungs and the brain is presented in this chapter. Such management remains a significant challenge to medical oncologists. Multidisciplinary evaluation and treatment approach is essential to improving the survival of selected patients with resectable metastatic disease, with multi-modal therapies designed to improve the long-term success of surgical resection. Better detection of molecular drivers of metastatic CRC has resulted from increased sophistication of molecular techniques. The use of correlative biomarkers in therapeutic clinical trials may identify subsets of the CRC population at increased risk of distant metastases, as well as subgroups likely to benefit from specific treatment combinations. In the era of biologic therapy and molecular oncology, patients

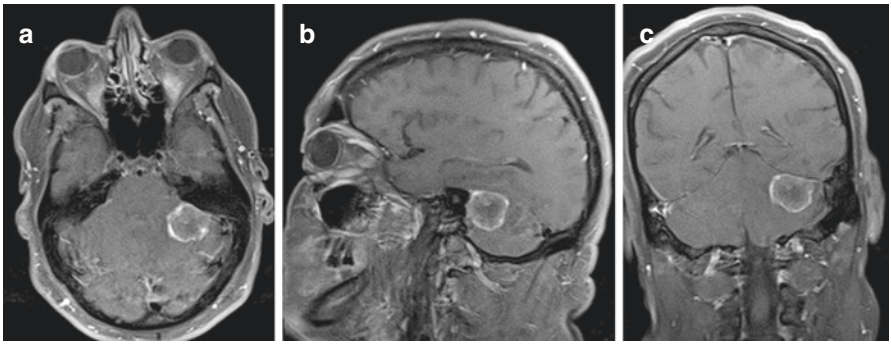

Fig. 25.1 MRI Brain: (**a**). Axial T1 image with contrast; (**b**). Sagittal image with contrast; (**c**). Coronal image with contrast
MRI images of a cerebellar brain metastasis in a 52 year-old male with KRAS wild-type rectal adenocarcinoma. The patient had previously undergone neoadjuvant chemoradiation followed by low anterior resection and ileostomy for rectal adenocarcinoma. One year later, he was diagnosed with a metastatic left lung lesion and underwent partial left lung resection. Following further regional recurrence 3 years after the initial diagnosis, he underwent pelvic exenteration for recurrent node-positive tumor with extension to the bladder, prostate, seminal vesicles and perirectal fat (moderately differentiated adenocarcinoma with lymphovascular invasion, Grade ypT4bN1aM1). One month later, he developed neurologic symptoms which included nystagmus, leading to the diagnosis of a left cerebellar lesion. After neurosurgical resection, histopathologic examination confirmed the tumor was KRAS wild-type metastatic adenocarcinoma, compatible with a colorectal primary malignancy. He received further systemic chemotherapy and was confirmed to be physically well with no evidence of recurrent disease more than 18 months after resection of the cerebellar metastasis

with rectal cancer – and with CRC in general – are living longer and thus the incidence of distant metastasis is likely to rise, making improvements in management approaches all the more essential to state-of-the-art practice. A recent paper by Ribeiro Gomes et al. [51] highlights the management of other unusual sites for CRC including the adrenal glands, the ovaries and the retroperitoneum.

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Chapter 26
Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy for Rectal Cancer

Todd M. Tuttle

Abbreviations

5-FU	5-fluorouracil
CC	Completeness of cytoreduction
CRS	Cytoreductive surgery
FOLFOX	Fluorouracil, leucovorin, and oxaliplatin
HIPEC	Hyperthermic intraperitoneal chemotherapy
LV	Leucovorin
PCI	Peritoneal Cancer Index

Introduction

The peritoneum is a common site of metastases from colorectal cancer. The treatment of peritoneal metastases has evolved from palliative care only to a potentially curative approach. Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has slowly emerged as an effective locoregional treatment for peritoneal metastases from a variety of malignancies, including colorectal cancer. Most studies combine colon and rectal cancer today as one malignancy: "colorectal cancer". In this respect, the majority of studies evaluating CRS plus HIPEC include only about 10–15% of patients with rectal cancer so that data concerning advanced peritoneal presentations of rectal cancer treated in this manner need to be viewed with caution. The purpose of this chapter is to review the incidence, treatment and outcomes of peritoneal metastases from colorectal cancer and when relevant from rectal cancer specifically.

T. M. Tuttle (✉)
Division of Surgical Oncology, University of Minnesota, Minneapolis, MN, USA
e-mail: tuttl006@umn.edu

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Incidence of Peritoneal Metastases

About 10–15% of patients with colorectal cancer will develop peritoneal metastases at some point during the course of their disease [1, 2]. Of those with peritoneal metastases, about two-thirds of patients present with synchronous metastases at the time of their initial diagnosis and about one-third of patients present with metachronous metastases. The reported incidence of peritoneal metastases from rectal cancer is slightly lower than for colonic cancer [2, 3]. The peritoneal surface is the only site of metastasis in about 50% of patients [1, 3]. Peritoneal metastases from colorectal cancer have been associated with identifiable risk factors including advanced tumor stage, advanced lymph node stage, venous invasion, mucinous adenocarcinoma, emergency surgery and non-radical resection [1, 2].

Survival Rates with Systemic Chemotherapy

The historical survival rates for patients with peritoneal metastases treated with palliative chemotherapy [5-fluouracil (5-FU) plus leucovorin (LV)] is poor. The median survival rates are about 6 months and few patients survive 5-years [1, 4]. However, more recent studies using modern chemotherapy (oxaliplatin and irinotecan) have demonstrated improved survival rates for patients with distant metastases from colorectal cancer. A study utilizing a pooled analysis of two phase III North Central Cancer Treatment Group studies in order to determine the survival outcomes of patients with colorectal cancer and peritoneal metastases [5] found a median overall survival rate of 12.7 months, and the 5-year overall survival rate was only 4.2%. For those who presented with small bowel obstruction, the median survival was less than 4 months. For patients treated with fluorouracil, leucovorin, and oxaliplatin (FOLFOX), the median survival rate was 15.7 months. In this study, the survival rate of patients with peritoneal metastases was significantly worse than the survival rate of those patients with other sites of distant metastases.

In another study (CAIRO1/CAIRO2) that analyzed the outcomes of patients with peritoneal metastases treated with modern chemotherapy with or without targeted agents, the overall median survival ranged from 10.4 to 15.2 months [6]. In this regard, even though the median number of treatment cycles were similar in those with or without peritoneal disease, there was a higher incidence of major toxicity in the peritoneal disease groups treated with sequential chemotherapy, although not toxicity that would normally result in cessation of treatment. The reduced efficacy of standard chemotherapy regimes in such patients therefore would not reflect undertreatment or increased overall toxicity susceptibility but rather tumor resistance to conventional treatment. So, even with modern chemotherapy, patients with peritoneal metastases from colorectal cancer still have a poor survival.

CRS Plus HIPEC

Cytoreductive surgery (CRS) plus hyperthermic intaperitoneal chemotherapy (HIPEC) has been increasingly used in the United States and Europe in an attempt to improve the survival rates of patients with peritoneal metastases from colorectal cancer. HIPEC was first described by John Spratt at the University of Louisville in 1980 as a "clinical delivery system for intraperitoneal hyperthermic chemotherapy" for a patient with pseudomyxoma peritonei [7]. In contrast to "debulking" surgery, CRS is a systematic attempt to remove all tumor nodules. The aim of HIPEC is to achieve high local concentrations of chemotherapeutic agents, combined with hyperthermia, to eradicate microscopic residual disease. Intraperitoneal delivery of chemotherapy achieves drug levels far higher than those which can be obtained with systemic chemotherapy. Theoretically, HIPEC is best administered immediately after CRS because all peritoneal surfaces are exposed, allowing a better drug distribution.

CRS is usually performed through a midline incision to remove all visible and palpable tumor nodules. Complete cytoreduction frequently requires multi-visceral resections and peritonectomy procedures. Peritonectomy procedures are usually performed only as indicated by the presence of visible tumor and have a specific categorization [8, 9]. A supracolic omentectomy is usually typically performed. Following optimal cytoreduction, the patient is prepared for HIPEC by passive cooling in order to achieve a core temperature of about 34–35 °C. There are different options here. In the closed procedure, two inflow catheters are placed percutaneously in the upper abdomen and two outflow catheters are placed in the lower abdomen and pelvis. Inflow and outflow temperature probes are similarly placed. The skin is closed so as to prevent leakage of the perfusate (Fig. 26.1). The perfusion is initiated at a temperature of 40–43 °C and flow rates are established and maintained at approximately 1 L/min. In the open technique ("Coliseum" technique), a silastic

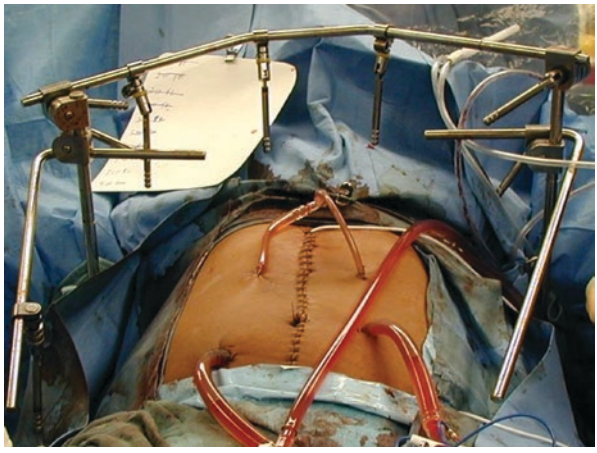

Fig. 26.1 Placement of intraperitoneal catheters for HIPEC

sheet is sutured over a retractor and to the patient's skin over the abdominal incision. This approach suspends the abdominal wall for instillation of the peritoneal perfusate. An incision is then made in the middle of the sheet to allow manual manipulation of the peritoneal perfusate.

An accurate assessment of the impact of CRS plus HIPEC on survival outcomes is limited by the lack of high quality data. Only one prospective randomized trial has been published comparing outcomes after CRS plus HIPEC with systemic chemotherapy for colorectal peritoneal metastases. In this single-center trial from the Netherlands Cancer Institute, 105 patients with peritoneal metastases from either colorectal or appendiceal cancer were randomized to palliative surgery plus 5-FU/LV (control arm) or to CRS plus HIPEC plus postoperative 5-FU/LV (experimental arm) [10]. In the HIPEC arm, patients received mitomycin C for 90 min. In the intention-to-treat analysis, CRS plus HIPEC was associated with a significant improvement in median survival (control arm, 12.6 months; experimental arm, 22.3 months, P = 0.032). The data also showed that those patients with less regional involvement of the peritoneal cavity after CRS had an overall better survival with improvement in survival if the CRS was at least macroscopically complete (R1) in nature as opposed to those clearances with limited (R-2a) or extensive residual (R-2b) disease.

In a subsequent publication of this trial with a median follow-up of about 8 years, the median disease-specific survival was still significantly improved in the experimental arm and the 5-year survival rate was 45% for patients who underwent complete CRS [11]. Importantly, there were only six patients with rectal cancer in the experimental arm. One of the major limitations of this single-center trial was that the chemotherapy (5-FU/LV) used in the control arm is not considered 'modern' chemotherapy although these results would suggest the possibility of long-term survival in a select group of aggressively treated patients.

Presently, there isn't a similar randomized clinical trial comparing CRS + HIPEC with modern chemotherapy. However, retrospective studies suggest a survival advantage for CRS plus HIPEC. In a study of 96 patients, Elias et al. [12] evaluated the outcomes of patients with peritoneal metastases from colorectal cancer treated either with modern chemotherapy (primarily irinotecan or oxaliplatin) or with CRS plus HIPEC. The patients in the chemotherapy alone arm had potentially resectable peritoneal metastases and no extraperitoneal disease. The median survival (23.9 *vs.* 62.7 months, respectively) and 5-year survival (13 *vs.* 51%, respectively) were significantly improved in the CRS plus HIPEC group when compared with the chemotherapy alone group.

Other retrospective studies have demonstrated that CRS plus HIPEC can yield long-term survival for selected patients with colorectal liver metastases. Chua and colleagues performed a systematic review of 19 studies published between 1995 and 2009 that included 2492 patients [13]. The overall median survival after CRS plus HIPEC was 33 months (range: 20–63 months) as compared with only 12.5 months (range: 5–24 months) for patients having palliative surgery and/or systemic chemotherapy. The respective median 5-year survival rates were 40% (range: 17 to 50%) and 13% (range: 13–22%). In a multicenter study of 660 patients, Glehen et al. reported a median overall survival rate of 30 months with a 5-year survival rate of 26% after CRS plus HIPEC [14]. In another multicenter study of

609 patients, Esquivel et al. reported a median overall survival of 41 months with a 5-year survival rate of 58% after CRS plus HIPEC [15].

The survival rates after CRS plus HIPEC appear to be similar for rectal and colon cancer patients. In one-single center study from North Carolina, the 3-year survival rates were 28.2% and 25.1% for rectal and colon cancer, respectively [16]. The authors concluded that selected rectal cancer patients with peritoneal metastases should not be excluded from attempted CRS plus HIPEC. In a multi-institutional study of 506 patients (including 40 patients with rectal cancer) treated with CRS plus HIPEC, the survival outcomes were not significantly different between those with colon and rectal cancer primary cancer [17].

Several factors predict survival outcomes following CRS plus HIPEC. The Completeness of Cytoreduction score as described by Jacquet and Sugarbaker in 1996 [18] is an important prognostic factor and is based upon the size of any residual tumor nodules after maximum cytoreduction so that: CC-0 is where there are no nodules; CC-1 has nodules <2.5 mm in maximal diameter; CC-2 has nodules between 2.5 mm and 2.5 cm and CC-3 has nodules >2.5 cm in diameter. In a French multicenter study, the median survival rates were significantly associated with CC scores; so that a CC-0 = 33 months; CC-1 = 20 months and CC-2/3 = 7 months [19]. Completeness of cytoreduction scores of CC-2 and CC-3 are associated with very poor outcomes and are considered contraindications for HIPEC.

Another important predictor of survival outcome is the Peritoneal Cancer Index (PCI). This score is determined intraoperatively and is based upon the size of tumor nodules and tumor distribution in 13 different regions of the peritoneal cavity [8, 18]. The PCI score also correlates well with survival such that a PCI value <12 is considered as low and that ≥12 is deemed moderate or high. In the French multicenter study headed by Dominique Elias at the Institute Gustave Roussy, the 5-year survival rates according to the respective PCI scores were: 1–6 = 44%; 7–12 = 22%; 13–19 = 29% and >19 = 7% [19]. Other predictors of survival include tumor grade, disease-free interval between diagnosis of the primary colorectal cancer and peritoneal metastases and patient age.

The contraindications for CRS plus HIPEC would include a poor general health status, the presence of extraperitoneal metastases and diffuse unresectable peritoneal metastases. Other relative contraindications include disease in the porta hepatis or around major vascular structures, a PCI index of >20, multiple levels of bowel obstruction, bilateral ureteric obstruction and biliary obstruction. Preoperative imaging often underestimates the extent of peritoneal metastases. In order to avoid a non-therapeutic laparotomy, diagnostic laparoscopy may be used so as to identify patients who are poor candidates for CRS plus HIPEC.

The two most commonly used drugs for HIPEC are mitomycin C and oxaliplatin. Mitomycin C is used primarily in the United States whereas oxaliplatin is use is more commonly throughout Europe. Prospective randomized studies comparing mitomycin C and oxaliplatin are not currently available. In a retrospective, multicenter study of 584 patients, Prada-Villaderde et al. reported that the median overall survival rates were not significantly different for the two main drugs (mitomycin C, 32.7 months *vs.* oxaliplatin, 31.4 months, respectively) [20]. However, the estimated cost of mitomycin C is about $180 compared with $18,000 for oxaliplatin.

CRS plus HIPEC is a major surgical procedure with considerable morbidity. In prospective trials from the Netherlands Cancer Institute, the operative mortality rate was 8% with a median estimated blood loss of 3.5 L. In the reported cohort there was the occurrence of grade 3–5 toxicities in 65% with an overall surgical complication rate of 35% [21]. An analysis on 2014 from the American College of Surgeons National Surgical Quality Improvement Program included 694 patients who underwent CRS plus HIPEC [22]. The overall complication rate was 33%, the mean length of hospital stay was 13 days, the re-admission rate was 11%, the reoperation rate was 9.8% and the mortality rate was 2.3%.

Prophylactic HIPEC Therapy

Thus far, this chapter has focused on the management of established peritoneal metastases. However, there is increasing interest in administering prophylactic HIPEC for high-risk patients who do not have established metastases. Elias et al. evaluated the outcomes of three high-risk groups; namely, patients who have a few tumor nodules resected along with the primary tumor; patients with ovarian metastases and patients who have perforated tumors [23]. For these three subgroups, a second-look operation was performed 1 year after the first surgical treatment and 6 months after the end of systemic adjuvant therapy. The benefit is in the detection of disease in the asymptomatic case which will be amenable to repeat resection. In this respect, asymptomatic peritoneal metastases were identified in 63%, 75%, and 33% of these respective subgroups. This study stimulated an on-going multicenter randomized trial in France (ProphyloCHIp -PRODIGE 15) that included these so designated high-risk patients. In this study, patients receive standard adjuvant systemic chemotherapy for 6 months and then are randomized to either surveillance or a second-look laparotomy with HIPEC [24].

Presently, the data assessing the effectiveness of prophylactic HIPEC are quite limited. One case-control study is available which included colorectal cancer patients with high-risk features for peritoneal metastases such as T3/T4 tumors, mucinous histology and signet ring cell histology. In this study by Sammartino from Sapienza in Rome, HIPEC was associated with a significant reduction in overall and peritoneal/local recurrence rates along with a significant improvement in overall survival, [25] suggesting a place for directed proactive therapy.

Conclusions

In summary, the peritoneum is a common site for colorectal cancer metastases. Even with modern chemotherapy, the survival of patients with peritoneal metastases is poor. Treatment with CRS plus HIPEC is associated with significant morbidity, but with improved survival. The median overall survival rate after complete

cytoreduction is about 30–50 months, and the 5-year survival rate is about 30–50%. The survival outcomes appear to be similar between colon and rectal cancers.

The lack of standardization of the technique of HIPEC has made it difficult to analyze the outcomes from centers performing this procedure throughout the United States and Europe. There is substantial variation in major components of HIPEC including: method of delivery (open or closed); drugs (oxaliplatin vs. mitomycin C); volume of perfusate; extent of hyperthermia (40–43 °C); and duration of perfusion (30–120 min). To minimize these variations, the American Society of Peritoneal Surface Malignancies published consensus guidelines to standardize HIPEC treatment [26].

Randomized clinical trials are needed to determine the benefit of key components of regional therapy. For example, does HIPEC add any value after CRS? In the French multicenter study Prodige 7, patients with colorectal peritoneal metastases undergo complete CRS and then are randomized to either HIPEC (oxaliplatin) or no HIPEC; patients in both arms receive any type of perioperative chemotherapy for 6 months.

HIPEC centers seem to be sprouting up all across the United States in both academic and community medical centers. These trends are concerning because several studies have demonstrated that operative and oncologic outcomes after CRS plus HIPEC are correlated with institutional experience [27, 28]. Authors from one high-volume academic center concluded that approximately 180 procedures were required to achieve the lowest risk of incomplete cytoreduction and severe morbidity, and approximately 90 cases were required to improve oncologic outcomes [23]. Perhaps, centers of excellence should be established and accredited to maximize patient outcomes.

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Part VIII
The Surgical Management of Recurrent Rectal Cancer

Chapter 27
The Management of Recurrent Rectal Cancer: A European Perspective

Giovanni M. Romano, Francesco Bianco, Silvia De Franciscis, and Andrea Belli

Introduction

Over recent decades there has been an extraordinary improvement in the management of rectal cancer leading to principally as an end-point to a marked reduction in the local recurrence rate. Thanks to the introduction in clinical practice of standardized total mesorectal excision (TME) and the implementation of both adjuvant and especially neo-adjuvant therapies, the incidence of local pelvic recurrence has effectively dropped from 20% to 30% down to an average of 6–10% and even lower in many dedicated colorectal units [1, 2]. These figures vary widely in population-based studies from 4% to 40% as well as in single-center and reported single surgeon series [2, 3]. The treatment of locally recurrent rectal cancer is still a major issue and a clinical challenge which deserves a multi-disciplinary approach and careful selection of patients suitable for surgery. Local recurrence generally occurs within the first 5 years after the primary surgery, with almost 70% of cases presenting within 2 years and 85% within the first 3 years [4, 5]. Nevertheless with the improvement in the effectiveness of adjuvant therapies and neoadjuvant chemoradiation (CRT) regimens, recurrences have been rarely reported to occur up to 10 years after the primary surgery [3].

The time interval between resection of the primary rectal cancer and presentation of the recurrence is considered an important prognostic factor where a short interval of less than 1 year is regarded as a generally poor prognostic factor reflecting the aggressive biology of the disease and the inadequacy of the primary surgery [6]. Up to 50% of patients with local pelvic recurrence also present with synchronous metastatic disease which includes recurrence within the para-aortic nodal basin. In the Dutch TME trial [7] 63% of patients with local recurrence also had distant metastases

G. M. Romano (✉) · F. Bianco · S. De Franciscis · A. Belli
Istituto Nazionale Tumori - "Fondazione G. Pascale" - IRCCS, Napoli, Italy

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whilst in the Swedish Rectal Cancer Trial [8] and in the Stockholm I trial [9] the percentage of patients presenting with synchronous local and systemic recurrences were 46% and 55%, respectively. Pelvic local recurrence can be localized to the lymphatic tissue draining the tumor (notably the pelvic side-wall lymph nodes or the residual mesorectal lymph nodes (less frequent after the introduction of TME) as well as in the tumor bed or at the anastomotic site. Recurrence can manifest itself also as a non-healing perineal wound or can be localized along the abdominal drain tract and at surgical scars [10].

Before the introduction of TME, local pelvic recurrence occurred often within the residual mesorectum or at the anastomotic site whereas nowadays with the widespread use of standardized TME as a technique and the administration of neo-adjuvant and adjuvant treatments in clinical practice, recurrences tend to have different patterns of presentation. This pattern difference over time has affected the surgical strategy, the true resectability rate and the likelihood of performance of an R0 repeat resection. Overall, these findings probably reflect the selection of more biologically aggressive tumors. At the present moment, there are no uniform guidelines for the management of locally recurrent rectal cancer (LRRC) so that patients with a local recurrence should be referred exclusively to tertiary centers with the requisite expertise and annual caseload volume needed in order to provide the patients with optimal treatment [11–14].

Clinical Presentation

The clinical presentation can frequently initially be asymptomatic and only incidentally discovered in up to 30% of patients or detected during regular follow-up programmes [10, 15]. The vast majority of patients are, however, symptomatic at the time of diagnosis [15] with changes in bowel habit, a sense of pelvic or abdominal discomfort, rectal bleeding (in the event of an intra-luminal mucosal recurrence) and pain as the principal reported symptoms. When the vagina is involved vaginal bleeding can occur and involvement of the bladder or the ureters results in hematuria or hydronephrosis. Bowel obstruction may also occur with neo-rectum invasion or with direct involvement of loops of small bowel within a pelvic mass. Pain can be present at presentation and is usually related to compression or infiltration of other organs, bones or neurovascular structures and its presence at the time of diagnosis is associated with a poorer overall prognosis [16].

Diagnosis

With the advent of more sophisticated imaging modalities and thanks to a better understanding of the natural history of resected rectal cancer, the need for an early diagnosis has become mandatory. Various clinical, histological, biological

and surgical factors have been associated with a higher risk of local recurrence, among them including T and N stage, the radicality and quality of the upfront surgery, the presence of a positive circumferential resection margin (CRM), the need initially for an abdominoperineal resection and any R1 or R2 resection. Added to this are various histological factors such as the formal tumor regression grade (TRG) after neoadjuvant therapy and the presence of vascular and/or neural invasion [6, 17–19]. Dedicated follow-up programs stratified for the risk of local recurrence should be implemented and an accurate analysis of risk factors should guide this process. An early diagnosis is feasibly related to a higher resectability rate which can ultimately offer patients a more optimal oncologic outcome. Valentini and colleagues [20], analyzing the results of 5 major European randomized trials of rectal cancer, established dedicated nomograms so as to stratify patients into risk groups for either local or distant recurrence, with the creation of prognostic scores for such event probability. These nomograms can potentially be used to guide the degree of dedicated follow-up in designated high-risk patients and to assist decision-making in selecting those suitable for postoperative adjuvant therapies.

The ideal diagnosis of locally recurrent rectal cancer is the histologic evaluation of the suspected tissue via percutaneous image-guided or endoscopic biopsy. A histologic evaluation of the suspected tissue can also assist in the discrimination of a truly neoplastic mass from a desmoplastic reaction or from fibrous tissue as part of a radiotherapeutic response. In many cases, however, accurate biopsy is not easy to obtain as opposed to those cases where endoscopy reveals at least a mucosal component to the recurrent lesion. Sometimes, in cases of late anastomotic leakage or in some pelvic infections, a differential diagnosis can be very challenging. When a positive biopsy is impossible to obtain, a clinical diagnosis as conducted by a specialized multidisciplinary team may be required to provide the consensus therapeutic approach, with the medicolegal consideration that at the time and with the available evidence, a specific course of treatment, including radical repeat resection, is collectively recommended [21]. Clinical evaluation of patients with suspected pelvic recurrence must include a digital anal examination which can help in discriminating between an extra-luminal and a luminal recurrence. Direct examination can also provide additional information about the fixity of the tumor as frequently can examination under anesthesia. In selected cases cystoscopy and vaginoscopy can also be useful in assessing the invasion of adjacent organs. Endoscopic US is not generally reliable in the assessment and staging of the recurrence, in particular in differentiating fibrous from neoplastic tissue and it may be affected in part by the endosonographic artefact of staples, by anastomotic distortion and by the sonographic impact of radiation which makes the submucosal discriminatory endosonographic layer appear relatively amorphous [22]. Plasma CEA levels are also frequently used with rapidly increasing levels associated with an overall worse prognosis [23, 24]. A rising CEA with equivocal CT and/or MR imaging may trigger an FDG PET-CT scan in the determination of a local recurrence [25].

Preoperative Evaluation and Staging

A complex multiple imaging staging process is generally needed in order to choose the optimal therapeutic strategy and to plan surgery [26]. A chest, abdomen and pelvis CT scan is preferred for both the determination of local pelvic extension of the disease and the sensitive detection of distant metastases. MRI, preferably with gadolinium enhanced contrast, is nowadays the gold standard in the assessment of the local extension and the grade of invasion of adjacent organs [27–30]. It can also be useful in discriminating between scar tissue, normal tissue and neoplastic tissue. Diffusion MRI and Dynamic Contrast Enhanced-MRI have both recently proved to be effective in discriminating residual neoplastic tissue in the setting of locally advanced primary rectal cancer pre-treated with radio-chemotherapy [31, 32]. These tools will most likely be extremely useful in the setting of suspected locally recurrent rectal cancer. PET-CT can also assist in the discovery of occult disease and in differentiating scar tissue from suspected neoplastic recurrence [33–36]. It can be particularly difficult to differentiate normal from neoplastic tissue during the first post-operative year especially in patients who have undergone neoadjuvant therapy or who have experienced significant post-operative septic pelvic complications. In both of these situations, the rate of false positive diagnoses can be especially high and in those cases where the diagnosis is uncertain short-term active monitoring is advisable with delay in PET-CT scanning for between 3 and 6 months where other indicators are in essence stable.

Accurate preoperative evaluation of the anatomical structures involved in the recurrence and a careful analysis of the surgical planes by an experienced surgical team is mandatory if radical repeat extirpative surgery is proposed. In this circumstance, there is a balance of operative risk with the likely predicted survival benefit and the expected impact on quality of life particularly in those cases with a poor overall risk for extended surgery or where there is a poor anticipated life expectancy either from the tumour itself or on life-table prediction from coincident comorbidity.

Classification

An agreed consensus classification of local pelvic recurrence would be extremely useful in guiding the multidisciplinary decision-making process and in stratifying patients into different prognostic groups. Unfortunately there is no current agreement concerning the extent and gradation of locoregional recurrence although various classification systems have been proposed most of which are based upon the anatomical site(s) of the recurrence, the different pelvic compartments involved and the variable degrees of tissue fixity. All of these classification systems aim to assist in surgical planning and to exclude those purely palliative cases where an R0 resection would be unlikely. This approach would provide a more standardized ability to counsel patients concerning their cancer-specific prognosis and survival expectancy.

In general, central recurrences tend to have a better overall prognosis in various prospective case series when compared with lateral and/or posterior recurrences. The principal current classification systems available are those American schemas (Mayo Clinic and Memorial Sloan Kettering Cancer Center- MSKCC), the Japanese classification system of Yamada et al. and the UK/European Royal Marsden Classification. The Mayo clinic classification [37] is mainly based upon the degree of fixity to anatomical structures located within the different pelvic compartments so that F0 is not fixed to any site; F1 is fixed to 1 site; F2 is fixed at 2 sites; F3 is fixed at ≥3 sites. In this system, the presence of symptoms and pain is also incorporated so that S0 patients are asymptomatic; S1 are symptomatic but without pain and S2 are symptomatic with pain. The presence of symptomatic pain and more than one point of fixation has proven to be associated with a significantly reduced cancer-specific survival in prospective series [16].

The classification proposed by MSKCC [23] takes into account the anatomical location of the mass and the structures involved in the recurrence. In this classification, recurrences are defined as axial, anterior, posterior and lateral with the relevant structures contained in the different pelvic compartments. By the aid of this system Moore and colleagues [23] demonstrated a very low probability of radical resection in cases where the recurrences were located in the lateral compartment. The Yamada classification [38] uses different grades of fixation patterns to classify recurrences into those which are localized (adjacent to connective tissue and organs), lateral and sacral. The different recurrence types (as so classified) have different 5-year survival rates ranging from 38% for the localized forms to 10% only for the sacral variants and nearly 0% in those cases of lateral recurrence. Recently, the Royal Marsden Hospital group has proposed a new classification system [39] with the aim of correlating the site of locoregional recurrence with the survival outcomes following surgical resection. This classification is based upon the degree of tumor invasion within the different pelvic compartments as visualized by preoperative MRI. In this setting the MR imaging of the pelvis is divided into 7 different compartments reflecting the different dissection planes between the pelvic organs and their fascial boundaries so that the division is as: Central (C), Posterior (P), Inferior (I), Anterior above (AA) and Anterior below (AB) the peritoneal reflection, Lateral (L) and at the Peritoneal reflection (PR). This latter classification is now widely used in Europe although it still needs prospective validation in a multicentre trial after having been advocated in a consensus agreement statement [39]. In general, however, all of these classification systems as mentioned concordantly show that central or axial recurrences are more frequently able to be adequately resected. Those tumours with a posterior location may require a concomitant bone resection in order to obtain an R0 tumour-free margin. Anteriorly located recurrences often require major exenterative resections and lateral recurrences tend to have lower resectability rates because of a greater chance of fixity to essential non-expendable structures. An agreed classification system would assist in the standardized terminology concerning extirpation and provide better data about prognosis and the comparative value of the different available surgical approaches.

Treatment

There are a number of different options for the treatment of locally recurrent rectal cancers which should be evaluated in the setting of a multidisciplinary team work-up of the single case. The location and the extent of the recurrence together with the evaluation of previously administered treatments must be taken into account in guiding the choice of the appropriate management strategy. Systemic chemotherapy, radiotherapy and chemoradiation and surgery alone or in combination can all play a role both in the setting of palliation and with the aim of achieving cure and long-term overall survival. In the vast majority of the studies 40–50% of patients with local recurrence are considered amenable to surgical exploration and 30–40% of them are reported to potentially be able to undergo an R0 resection [2, 3]. This would imply that just 20–30% of patients with recurrent rectal cancer will undergo a potentially curative resection, however, this data are affected by the selection criteria and the surgical expertise of the different institutions. We commend some broad general principles regarding this eclectic patient group.

The Role of Radiotherapy

Nowadays, radiotherapy (RT) has a major role both in obtaining symptom relief and local control of the disease. The use of RT has been historically limited in cases of recurrence in those patients who had received previous high-dosage pelvic irradiation. In the case of patients not previously irradiated, RT can play a role in the neoadjuvant setting with the aim of increasing the proportion of patients potentially suitable for radical surgery. High-dose (50–60 Gy) RT also in combination with chemotherapy is generally administered and had been proven to convert cases towards radical resectability in up to 80% of patients initially not amenable to surgical exploration [40]. The ability to achieve a target radiation dose (45–50.4 Gy) in such RT-naïve cases has been associated with survival advantage [41]. Recently, a variety of international experiences have been reported showing good results of re-irradiation of the pelvis both in terms of oncologic outcomes and in the rates of radical resection [42]. Several centers have reported the possibility of administration of an additional hyper-fractionated chemoradiation (up to 30 Gy) in selected cases without severe morbidity [43]. In this respect, Valentini et al. [44] reported in a phase II study their experience with 59 patients undergoing iterative pelvic irradiation with hyperfractionated chemoradiation before surgical resection showing a very low rate of acute complications with excellent pain control [44]. In their series 35% of patients underwent an R0 resection with a 5-year overall survival of 39%.

Endorectal beam therapy as an option is not commonly used in Europe, but it also can play a role especially in cases of centrally-located recurrences. Moreover, the role of intra-operative radiation therapy (IORT) which is not widely available in the multimodal treatment of locally recurrent rectal cancer is still controversial.

The advantage here is to deliver a boost to the marked tumour bed after repeat resection with the majority of studies reporting IORT electron beam therapy. The technique permits the use of customized flexible applicators for precise delivery of up to 5Gy at a single sitting with application where surgical margins are considered close (e.g. near the bony side-wall) [45, 46]. This approach may be combined with protocolized treatment in combination with external beam radiotherapy (EBRT) and chemotherapy. When compared with EBRT and surgery the combination of IORT, EBRT and surgery does not appear to add any significant morbidity where a total of 30 GY can be administered safely [47]. At the moment, no definitive conclusions can be drawn since the limited number of patients included in the published studies and the controversial results of the effect of the addition of IORT to standard treatments is not currently associated with high-grade evidence. In this regard, whilst a Heidelberg study by Treiber et al. [48] has reported an improvement in local control with the addition of IORT to EBRT plus surgery, another Norwegian report by Wiig and colleagues [49] failed to demonstrate any beneficial effect of IORT both on local control and cancer-specific survival.

The Role of Surgery

Surgery alone or in the setting of a multimodal approach is still the benchmark of the treatment of locally recurrent rectal cancer and is the only option which can potentially offer cure and long-term survival. An R0 resection should be the goal of surgery where accurate pre-operative planning is mandatory since such radical extirpative surgery remains compromised by a high complication rate and a non-negligible mortality rate in cases of major exenterative surgery. In patients deemed unresectable or in those with systemic disease, surgery can still selectively also have a role in the palliation of some pelvic complications. Concomitant systemic disease is generally considered a contraindication where surgery is reserved in the case of highly selected symptomatic patients with a limited tumor burden and in which radical resection can be obtained [50–52]. In cases of concomitant extra-pelvic disease preoperative chemotherapy can help in testing the tumour responsiveness and aggressiveness. Provided that a radical resection of both pelvic and extra-pelvic disease can be attempted surgery should be reserved for young fit patients since the long-term outcomes of this policy are still unclear. Recent standardization of specific symptoms and their improvement may be more objectively made in the future paying specific attention to symptom burden, most notably, pain, eating (loss of appetitie and weight loss), physical impairment, social needs and psychological suffering (anxiety/burden of disease/depression) [53].

Some authors have reported acceptable survival in selected patients with limited extra-pelvic disease (mainly liver metastases) achieving a 5-year survival of 42% in patients who had undergone an R0 resection [54, 55]. The commonest contraindication to surgery is a predictably low probability of obtaining an *en-bloc* radical resection and this is most often the case in recurrences involving the lateral pelvic

side-walls where there is iliac vessel(s) involvement, lower limb edema and/or the infiltration of either the obturator or the sciatic nerve (and lumbosacral neural plexus). In very selected cases reported by a few authors [56, 57] there is a limited experience with *en-bloc* vascular resection and reconstruction or *en bloc* external hemipelvectomy or hindquarter amputation in those cases where there is neurovascular infiltration at the point of the greater sciatic notch/foramen. The use of this extremely aggressive approach is very limited at the moment since it generally carries a precluding high morbidity with functional and cosmetic disadvantages and no real impact on overall survival.

As additional caveats:

1. Hydronephrosis has also been considered a contraindication to radical surgery by some authors but is generally not considered so in the vast majority of dedicated centers.
2. The presence of neural pain has been reported to be a factor which negatively impacts both the R0 resection rate and oncologic outcomes [58].
3. Extremely obese patients or the very elderly need very careful consideration because of the attendant morbidity and mortality [59].

The Surgical Approaches to Locally Recurrent Rectal Cancer

In the era of TME, the clinical and pathological features of local recurrences have drastically changed. In the pre-TME era, local recurrences often occurred within the residual mesorectum (left behind at the first operation) and presented at the anastomotic site. By contrast, nowadays local recurrences of rectal cancer are not generally confined to the perirectal area and can be localized to any pelvic compartment. This new presentation of locoregional recurrence depicts a new scenario in which any pelvic structure can be involved often resulting in the need for extended surgery and multimodal treatment. In general, a surgical approach more similar to that of sarcoma surgery has been suggested by several authors [60].

As already mentioned, the extent of surgery is guided by the location and the nature of the recurrence. In the case of early diagnosis of mobile recurrences located at the anastomotic site, either in the central compartment of the pelvis or at the perineal wound, a radical resection can be generally achieved with limited surgery (an abdomino-perineal resection or a local resection). If the recurrence is located in a narrow pelvis and a salvage abdomino-perineal resection is needed, the resection plane should pass outside the levator plate in order to obtain a cylindrical specimen and to maximize the radicality of the procedure [61]. Unfortunately, in the post-TME era, recurrent tumors are often located in the narrow part of the pelvis and may present as a fixed mass invading the pelvic side-wall. The surgical treatment of fixed recurrences is a significant challenge which may require major multivisceral resections. In this setting a complex surgical team including colorectal surgeons, urologists, orthopedists, gynecologists and plastic surgeons is frequently necessary since there may be a requirement for bony (sacral and coccygeal) resection(s), bladder or

prostate resection and a hysterectomy and a partial or total colpectomy so as to obtain complete tumor clearance. If the recurrence is anteriorly located, a total pelvic exenteration is generally an adequate procedure in obtaining radical margins. When extensive bladder involvement is present or if the recurrence involves the trigone of the bladder, a total cystectomy is needed. In this case with a urinary diversion being created generally with formation of an anastomosis between the ureters and the last loop of small bowel (a Bricker's procedure).

Many patients have recurrences located in the lateral or the dorsal compartment of the pelvis. Obtaining tumor free margins in these cases can be extremely demanding and sometimes impossible by virtue of involvement of the major vessels or the bony part of the lateral pelvic wall. When the recurrence is located in the dorsal compartment, abdomino-sacral resection can be performed. In general, limited bony resections are confined to the distal segments below S2 which are preferred since they generally carry a lower risk of surgical complications with a better expected quality of life. The usefulness and the extent of concomitant sacral resection has been a matter of debate in recent years since the procedure can carry a high risk of serious neuropathy as well as the attendant intraoperative risks related to uncontrollable venous bleeding. Wanebo and colleagues were the first to report abdomino-sacral amputation with high sacrectomy for recurrent rectal cancer in 1981 describing a technique similar to that used for sarcomas [62]. In their original paper on 53 patients, they reported an 8% of intra-operative mortality with a mean blood loss of more than 8 l. The 5-year survival rate in this cohort was 31%. Similarly, Moriya and colleagues reported in 2004 their experience with distal sacrectomy (lower than S2) in 57 patients, showing a better mortality rate (3.5%) a lower intraoperative blood loss and a 5-year survival rate of 46% [63].

Recently Bhangu and colleagues have published the outcomes of abdomino-sacral resection for locally advanced or recurrent rectal cancer in 30 patients (22 locally recurrent cases) reporting a 77% R0 resection rate and a 5-year overall survival of 55% [64]. In their series, high sacrectomy (at S1/2) was associated with more frequent, multiple and serious adverse events than mid-level and low sacrectomy. In 2013 Milne et al. [65] assessed in a series of 79 patients, the impact of concomitant sacral resection on morbidity and survival in those undergoing extended surgery for locally recurrent rectal cancer The authors reported an R0 resection rate of 74% with no 30-day mortality but a morbidity rate approaching 80%. In this study, the level of sacrectomy (< *vs*. > S3) did not affect the complication rate and the 5-year overall survival was 45 months and 19 months for patients undergoing either an R0 or an R1 resection, respectively.

Mortality and Morbidity

The rate of surgical-related mortality and morbidity is obviously influenced by accurate patient selection and the extent of the surgery performed which itself is affected by the pelvic location of the recurrence. In a systematic review by Tanis

et al. [66] analyzing 46 studies concerning the surgical treatment of locoregional recurrent rectal cancer, there was an average mortality of 2.2% (57 of 2515 patients) in the pooled series with a substantial improvement in overall cancer-specific survival over time. It is suggested that a greater uniformity in the treatment protocols may account for some of these better findings along with an improvement in patient selection and the broader utilization of multimodality treatments. Abdomino-sacral resection is the procedure with the greater incidence of complications and surgically-related deaths. Common post-operative complications include intestinal obstruction, urinary and enteric leakages/fistulae, pelvic abscesses and perineal zone infections as well as systemic complications such as sepsis with multi-organ failure and pulmonary embolism [67]. When an abdomino-perineal excision (APE) is performed or an APE is combined with a sacral resection, the commonest problem is perineal wound dehiscence and infection. This complication can be minimized particularly in the irradiated case with the use of myocutaneous flaps or selective biological meshes. A non-healing wound can also benefit from the use of vacuum assisted medicated systems [68].

Oncologic Outcomes

Without an attempt at resection the overall survival of patients with locally recurrent rectal cancer is lower than 5% at 5 years with a median survival of approximately 7 months [67]. In a study by Nielsen and colleagues [69] which systematically analyzed the oncologic outcomes of patients submitted to surgery for locally recurrent rectal cancer derived from 19 studies, the 5-year overall survival was reported in 12 studies and varied between 9% and 39% with a median survival ranging between 21 and 55 months. It is accepted in such a systematic analysis that there is considerable study heterogeneity and that the survival outcomes depend upon the different selection criteria used between institutions and the specific aggressiveness of the surgical policy adopted in individual centers. Nevertheless, a clear benefit for surgical resection is evident in patients deemed suitable for radical surgery where R0 resection is widely reported as the strongest prognostic factor affecting survival. In a systematic review by Tanis and colleagues [66] the 5-year overall survival ranged from 11% to 51% and the 5-year survival was at least 25% in 11 of 18 studies including at least 50 resections. Similarly, Rahbari et al. [55] reported the outcomes of an aggressive surgical policy at a European center in patients with locally recurrent rectal cancer in the post-TME era where 107 patients were evaluated for surgery with 92 undergoing resection with an R0 rate of 58.7%. Disease specific survivals were 61% and 47% at 3 and 5 years, respectively with a reported promising 3-year overall survival of 42% for patients with extra-pelvic disease who underwent radical resection.

Banghu and colleagues presented in 2014 an important case series [70] of 100 patients who underwent pelvic exentaration for locally advanced or recurrent rectal cancer (45 patients) and this is currently the most up-to-date European experience. In this study, patients naïve to chemoradiation were offered long-course treatment

whilst patients previously receiving pelvic irradiation were offered an additional radiotherapy boost to the margin of planned resection, evaluating each treatment case by case (which is the current trend in many European centres including our own institution). All patients were re-staged with MRI after 6–8 weeks from the end of radiotherapy. In the reported study, the 30 day mortality was 0% with 53% of the patients experiencing at least one adverse event with concomitant sacrectomy (22 cases for locally recurrent rectal cancer). This procedure was associated with a longer operating time, a higher intra-operative blood loss and a longer length of hospital stay. R0 resection proved to be the most important factor contributing to overall survival (65% at 5 years for locally recurrent rectal cancer). Nevertheless, an R1 resection seems to also have a role in prolonging survival and reducing symptoms. In the study by Nielsen and colleagues [71], another important European experience was reported focusing on the prospective evaluation of 90 patients undergoing total pelvic exenteration for advanced primary and locally recurrent rectal cancer (n = 40 with local recurrence). The R0 resection rate was 36% in the locally recurrent cases and the radicality of the procedure strongly related to the oncologic outcomes. The disease-free survival and overall survival at 3 years were 22% and 40%, respectively. Again this study proved that in selected centres total pelvic exenteration can be offered with low mortality and an acceptable morbidity justifying the procedure also specifically for rectal cancer recurrence.

At our Institution, 44 patients underwent surgical resection for locally recurrent rectal cancer. The perioperative mortality was 7% (three patients) whilst 23 patients experienced at least one adverse event (52%). An R0 resection margin was obtained in 34 cases as a result of a very strict selection policy. With a median follow-up of 4 years, patients undergoing a radical resection have a survival rate of 36% which is in accordance with other international series.

Quality of Life Considerations

There is comparatively little available data concerning the quality of life in patients undergoing extensive surgical resection for recurrent rectal cancer. Despite this, however, it is clear that from the patient's point of view that a major exenterative operation will deeply affect the self-perception and drastically change the body image and life style. The urinary function when a urinary diversion is performed is a major quality of life issue, as is the postoperative sexual function particularly when a neovaginal reconstruction is fashioned. Equally, bowel habit especially after a colo-anal anastomosis has a major impact on reported quality of life parameters. In the case of a sacral resection, the section of S2-S3 nerve roots will cause bladder denervation and motor disturbance of the sciatic nerve. Section of the S1 roots causes ambulation problems because of a deficit in plantar flexion. Active and extensive information about potential complications and permanent deficits must be provided by physicians and the patients should be actively involved in the decision process after the provision of such specific information based on the level and type

of recurrence and imaging data so that they can carefully analyze and understand the benefits and drawbacks of the proposed surgery. In a study by Palmer and colleagues [72] patients were evaluated before and after surgery at 18 months with the EORTC questionnaires QLQ 30 and QLQ CR 38. Those patients treated with extensive surgery referred defaecatory symptoms, social impairment, a higher degree of pain and fatigue as well as impaired self-perception. In a similar study by Esnaola et al. [73] patients operated for locally recurrent rectal cancer were compared with patients who underwent palliative treatments only, showing a comparative impairment in the quality of life-related outcomes and moderate pain scores during the first 3 years after surgery.

By contrast, however, in a study by Guren et al. [74] from Oslo, the presence of a urostomy in addition to a terminal colostomy did not appear to significantly worsen the quality of life in comparison to those patients without urinary diversion. These studies are affected by the fact that there is no uniformity in the instruments used to measure the quality of life and all the included studies have a methodological bias with a focus generally on small numbers of patients where in a systematic analysis performed by Thaysen et al. [75] the sample size varied from 12 to 44 patients. A crucial point is to deliberately inform all patients about the nature of possible complications and predicted changes in life-style and self-perception, since some of the operated patients will ultimately undergo prolonged hospital stays and possible repeat surgery for surgical-related complications or a re-recurrence of disease.

Conclusions

The best treatment for recurrent rectal cancer is of course its prevention through the choice of the optimal therapeutic strategy at the time of the primary rectal cancer presentation. In this respect, the best treatment starts from an accurate staging in order to stratify patients into different prognostic groups which deserve a tailored approach recommended by a specialist multidisciplinary team conducting a high volume of complex rectal cancer surgeries and ancillary treatment programs.

Pre-operative radiotherapy and chemoradiation has proven to be the current gold-standard for the treatment of locally advanced low-rectal cancer but the optimal interval to surgery is still uncertain, potentially influencing the local recurrence rate. A strong case can be made for reserving rectal cancer surgery to specialized high-volume centers where an optimal TME with a low rate of intraoperative perforation and post-operative morbidity can be offered with the highest R0 resection rate [76]. An adequate and long-term follow-up strategy is of course crucial in the post-operative period since an early diagnosis of recurrence can obviously affect the ultimate cure rate. Once diagnosis has been established, accurate staging with modern imaging modalities should be undertaken and a multidisciplinary team assessment is mandatory in order to select patients who can benefit from surgical resection and/or from radiotherapy or systemic and palliative treatments. Major exenterative

surgery is often needed to obtain radical resection with histologic resection margins being the strongest prognostic factor associated with long-term survival. The modern surgical approach to the treatment of locally recurrent rectal cancer resembles the principles adopted for sarcoma surgery and follows unconventional dissection planes with pelvic dissection generally conducted beyond the fascia propria of the mesorectal envelope. An accurate balance between the potential benefits of surgery and the high related morbidity associated has to be made since for the moment, only one-third of patients brought to the operating room will undergo an R0 resection and many will experience complications which require long-term hospitalization.

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Chapter 28
The Management of Recurrent Rectal Cancer: A North American Perspective

Antonia Henry and Ronald Bleday

Introduction

An estimated 40,000 new cases of rectal cancer will be diagnosed in the United States in 2015 [1]. Of those, several thousand will have locoregional recurrence. The introduction of total mesorectal excision (TME) decreased the chance of local recurrence from 13.5% to 25% with conventional surgery and adjuvant chemoradiotherapy down to 5–10% [2–4]. Up to 50% of those with local recurrence do not, however, have disseminated disease [2]. The median time to recurrence is 16 months usually presenting with symptoms such as pain and rectal bleeding [4]. Longer times to recurrence are associated with decreased risk of repeat recurrence and a longer disease-free survival after salvage treatment [5]. This chapter examines the risk factors for recurrence, the selection criteria for treatment of recurrent rectal cancer and the types of operative interventions.

Risk Factors for Recurrence

Tumor Histology, Tumor Margin and Location of the Cancer

Recurrence after rectal cancer surgery is uncommon and prognosis is poor without surgery. Unfavorable histology in the primary tumor such as poor differentiation, lymphovascular invasion, perineural invasion, positive circumferential margin, and

A. Henry
Naval Medical Center, San Diego, CA, USA

R. Bleday (✉)
Section of Colon and Rectal Surgery, Brigham and Women's Hospital, Boston, MA, USA
e-mail: rbleday@partners.org

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tumor budding have all been associated with recurrence. In a case control study, Dresen et al. compared 92 patients who developed locally recurrent rectal cancer with 185 patients without recurrence and found that lymphovascular invasion, extramural venous invasion, a positive circumferential margin, and poor differentiation were all significantly associated with local recurrence [6]. The intensity of tumor budding, which also correlated with local recurrence, may reflect the biologic aggressiveness of the tumor [7].

Involvement of the circumferential margin is strongly correlated with recurrence. The extent of invasion into the mesorectum has been identified as a powerful independent predictor of local recurrence along with venous and lymphatic invasion, with high risk for a circumferential margin ≤1 mm in patients with pT3 or pT4 rectal cancers [8]. In addition to predicting local recurrence, a positive margin is associated with over 3 times the chance of developing a distant metastasis (40% *vs.*12%) along with decreased survival (hazard ratio for mortality 3.7, 95% CI 1.7–8.4) potentially impacting the selection of patients for postoperative adjuvant therapy [9]. Further, neoadjuvant radiotherapy is not protective against local recurrence in those cases with a positive circumferential margin [10].

Tumors located in the distal third of the rectum were found to have significantly higher recurrence rates than those in the middle or upper third [4]. The more unfavorable prognosis of lower rectal cancers may be related to an increased chance in particular of regional spread to the lateral pelvic side wall. In Japan, lateral pelvic lymph node dissection has been performed in conjunction with total mesorectal excision for low rectal cancers. This issue is discussed elsewhere in this book. In this regard, an intraoperative study to detect rectal lymphatic drainage in patients with low rectal cancers using colloid radioactive tracer found that pelvic lymphatic flow to the lateral pelvic sidewall outside the mesorectum was detected in 28% of patients. In these cases, tumor cells were histologically identified in the lateral pelvic lymph nodes of 36% of the patients studied. Although lateral pelvic lymph node dissection has not been proven to offer a survival benefit, the use of neoadjuvant and adjuvant chemotherapy in patients with evidence of lymphatic spread to the lateral pelvic side walls may improve outcomes [11]. In this setting, poor prognosis patients with tumor cells extending beyond the fascia propria recti with associated lateral pelvic lymphatic flow will benefit from preoperative chemoradiation. Preoperative CT scan detection of lateral lymph nodes >6 mm in diameter has been correlated with malignant involvement [12] and may also help guide therapy. Finally, lateral pelvic and perirectal lymph node metastases are independent risk factors for local recurrence among patients undergoing pelvic sidewall dissection in addition to total mesorectal excision [13]. Here, although the number of patients with advanced disease is greater in series biased towards side-wall pelvic dissection, there are frequently no differences in their local recurrence rates (even when tumor category is considered in analysis) suggesting benefit in lateral lymphadenectomy. In many of these studies, failure to perform a side-wall lymph node excision is associated with a poor prognosis, recommending value in the performance of future randomized controlled multi-institutional studies in order to address this issue [14].

Impact of Total Mesorectal Excision on the Risk of Recurrence

Local recurrence rates following curative low anterior resection have been found to be 5–8% with overall survival up to 80% at 10 years [15]. Approximately half of the local recurrences were located at the anastomosis and the other half were pelvic sidewall recurrences [16]. Among the 380 patients undergoing TME in Heald's series, extramural venous invasion was a significant predictor of local recurrence, whereas the Dukes stage, tumor grade, anastomotic leak rate, height of tumor above the dentate line, or anastomotic height did not significantly influence local recurrence [15]. Of note, the majority of these patients did not receive neoadjuvant chemoradiation. However, although TME seemed to be protective against local recurrence it was not protective against distant recurrence. In a study of 297 patients with T3-4 or N1 tumors treated with neoadjuvant chemoradiotherapy and TME, 67 (23%) had local or distant recurrence. Most of the failures, 19%, were isolated distant recurrences and only 2% were isolated local recurrences [17].

Local Recurrence: Local Excision Versus Radical Resection

Recurrence after local excision is somewhat higher than after radical resection. In a population based study of 2318 patients with rectal cancer from Sweden reported by Palmer et al. and managed with local excision or proctectomy, 141 were found to have local recurrence [4]. In this study, those managed with primary local excision were more likely to develop local recurrence, (12% *vs.* 7%, respectively). In a series of 29 patients reported by Hompes et al. residual tumor or involved lymph nodes were found in 47% of completion TME specimens performed after local excision for tumors with unfavorable pathology or positive margins [18]. A recent Canadian meta-analysis by Kidane and colleagues of 1426 patients with T1 rectal cancers in 12 observational studies evaluating 5-year disease-free survival, radical resection was favored when compared with both transanal excision and transanal endoscopic microsurgery (RR 1.54, 95% CI 1.15–2.05) [19]. Analysis of long-term outcomes in a prospective, multi-institutional study assessing local excision of distal rectal adenocarcinoma found that local recurrence rates for patients with T1 lesions treated with local excision and T2 lesions treated with a combination of local excision and adjuvant chemoradiation were 8 and 18%, respectively, with rates of distant metastases 5% for T1 and 12% for the T2 lesions [20]. For T2N0M0 cancers, if the order of treatment is reversed, where the neoadjuvant therapy is followed by local excision, then the local recurrence rates drop down to 4% [21].

In this respect, Weiser et al. have evaluated local recurrence following transanal excision in 50 patients initially diagnosed with T1–2 rectal cancer. The majority of patients with recurrence were able to undergo salvage resection, but 55% required an extended pelvic dissection with *en bloc* resection of adjacent pelvic organs in

order to achieve an R0 resection. The 5-year disease-specific survival was 53% in this study [22]. These results have been recently corroborated by a study from the Mayo Clinic of 27 patients who experienced locally recurrent disease after local excision for early rectal cancer. The majority, 93% of cases were able to undergo an R0 resection, but the 5-year overall survival was only 50% with a 5-year repeat recurrence-free survival of 47% [23].

Unfavorable pathologic features of the primary tumor can increase the risk of mesorectal metastases and local recurrence. Options for salvage surgery after local excision include repeat full-thickness excision or radical resection. While organ preserving options offer decreased early morbidity and may be appropriate for elderly or medically unfit patients, salvage radical resection decreases local recurrence.

Sequence of Therapy

The benefit of preoperative radiotherapy for local recurrence in rectal cancer treated with TME was demonstrated by the Dutch Colorectal Cancer Group. Of the 1748 patients who had a macroscopically negative resection, the 2-year local recurrence rate was 2.4% in the radiotherapy plus TME group *vs.* 8.2% in the TME only group ($P < .0001$). In subgroup analyses, the addition of preoperative radiotherapy reduced the risk of local recurrence significantly in patients who had tumors ≤10 cm from the anal verge or who were TNM stage II or III [24]. The benefit of preoperative radiotherapy persisted with longer follow-up but did not result in a survival benefit [25].

Surgeon Experience

Prior research has shown that patients managed by higher volume surgeons (≥12 rectal cancer resections annually) have lower rates of local recurrence (4% vs. 10%) and lower cancer-specific mortality (11% vs. 18%) [26]. Colorectal surgical subspecialty training and higher surgeon-specific volume were found to benefit patients with rectal cancer as local recurrence and disease-specific mortality were increased in patients operated on by non-specialty trained surgeons and those who performed fewer than 21 resections annually [27]. Greater experience among specialty-trained surgeons was also found to improve outcomes in the Stockholm Rectal Cancer Study Group. Patients undergoing rectal cancer surgery by colorectal surgeons with at least 10 years of experience had a lower risk of recurrence and death from rectal cancer [28]. Surgeon training, experience and operative volume may be associated with the quality of a TME. In a quality assurance study, the integrity of the mesorectal dissection was an important predictor of local and distant recurrence [29].

Diagnostic Evaluation of Recurrent Rectal Cancer

Diagnostic evaluation of recurrent rectal cancer should begin with a physical exam to assess invasion of the tumor into nearby structures in order to determine resectability. Digital rectal exam can demonstrate recurrence along the suture line in a low anastomosis, involvement of the anal sphincter, or an impression of extramural fullness which may be a sign of recurrence in the mesorectum. A pelvic exam can determine fixation of the recurrence to the posterior vagina in women. Bony pain or neural involvement suggests invasion into the lateral pelvic side-wall or sacrum.

Imaging is essential for selecting candidates for operative intervention. Endorectal ultrasound (ERUS), multi-detector computed tomography (MDCT), magnetic resonance imaging (MRI) and positron emission tomography–computed tomography (PET-CT) can be used to evaluate the presence and extent of local recurrence.

ERUS can be performed if the lumen of the rectum is not narrowed and distorted by the tumor. Although it is highly sensitive and specific for staging primary T4 tumors (sensitivity 95.4%, specificity 98.3%), there are significant limitations for the patient who has previously been treated with radiation and surgery [30]. Radiation therapy can cause peritumoral inflammation, resulting in the rectal wall becoming thickened and more hypo-echoic and making it difficult to distinguish the individual layers of the rectal wall with ERUS for up to a period of 12 months after treatment [31]. Postoperative scarring, tissue distortion, displacement of adjacent organs, and the sequelae of local sepsis can all complicate interpretation of postoperative images [32]. The addition of color Doppler imaging can be a useful adjunct in distinguishing recurrent tumor from postsurgical scarring [33].

CT of the chest, abdomen and pelvis is recommended to evaluate distant spread but local recurrence may not be seen on a post-operative surveillance CT. The attenuation of post-operative or post-radiation fibrosis may be the same as that of recurrent rectal cancer [34]. CT-guided biopsy can be used to differentiate fibrosis and scarring from tumor [35]. CT may be more useful for assessing the involvement of adjacent organs, fixation to the pelvic side-wall and resectability. CT has been shown to be 85% accurate in predicting resectability and invasion into the sacrum or the uterus, but may overestimate involvement of the bladder [36].

Contrast-enhanced MRI is the recommended modality for preoperative imaging of recurrent rectal cancer [37]. MRI is more accurate in distinguishing scar and irradiated tissue from tumor [38, 39]. While T2-weighted imaging is the main sequence for initial staging of rectal cancer, it is not specific enough for assessing recurrence. On T2-weighted images, recurrence appears hyperintense and is not distinguishable from early postoperative or post-radiation inflammation and edema [40]. Contrast enhancement of tumor has been shown to occur earlier and to be more intense and heterogeneous than in benign post-treatment fibrosis [41]. MRI is also more sensitive and accurate than CT for detecting sacral bone marrow involvement [42]. The reported sensitivity of CT for identifying local recurrence is 82–91% and its specificity is 69–72%, while the sensitivity of MRI is 80–90% and its

specificity is as high as 100% [43–45]. Diffusion-weighted MRI fuses anatomic MRI with diffusion-weighted imaging, and may be better able to detect recurrence [43].

The addition of PET-CT can be used selectively to distinguish scar from tumor and has greater sensitivity, specificity and accuracy than PET alone for the diagnosis of recurrent rectal cancer [46]. In a meta-analysis by Zhang et al. of the diagnostic value of PET in assessing recurrent rectal cancer, the pooled sensitivity and specificity for detecting hepatic metastasis were 97% and 98% [47]. The pooled sensitivity and specificity for pelvic metastasis or local regional recurrence were 94% and 94% in this study. However, in our experience PET scans have a high false positive rate in patients with either a colon J pouch or a side-to-end anastomosis where the blind end of these anastomoses shows high, false positive, FDG activity.

Treatment/Outcomes

During multidisciplinary assessment of the patient for resection, several issues must be addressed. Curative resection of intraluminal recurrences is more often achieved than in extraluminal recurrence and is also associated with longer survival [48]. In general, anterior invasion into the genitourinary structures or posterior invasion into the coccyx or lower sacrum are more favorable prognostic indicators than lateral pelvic side-wall involvement because of the increased likelihood of attaining an R0 resection. High sacrectomy for disease more proximal than S3 decreases the chance of an R0 resection. Bilateral hydronephrosis may indicate involvement of the ureters at the trigone. Unilateral hydronephrosis can also indicate unresectable recurrence into the upper pelvic sidewall near the pelvic brim. Other unfavorable anatomic features include lateral pelvic bony invasion, fecal incontinence and obstruction.

Surgical Technique

Resectability: General Principles

Pre-operative planning will involve review of all pertinent imaging in order to evaluate the potential involvement of adjacent structures. Based on the location of the recurrence, the assistance of additional specialists in Urology, Orthopedic Spine Surgery and Vascular Surgery may be needed. The objective of operative intervention for local recurrence is *en bloc* removal of all involved structures to obtain an R0 resection. Intraoperative frozen section may be useful to confirm negative margins [49]. The patient should meet with an enterostomal therapist pre-operatively to select appropriate sites for a colostomy and/or urostomy. If sacrectomy is planned, radiological tattooing of external anatomy can be considered to define the level of the sacrectomy [39]. Pre-operative placement of ureteral stents will help to identify

the ureters given the obscured anatomy resulting from prior operations and pelvic irradiation [39, 42, 49]. Operating room equipment should include long instruments, head lights, and lighted retractors [39].

Laparotomy begins with an initial exploration to check for peritoneal or distant metastases in the abdomen and assessment of resectability [39, 42, 49, 50]. If ascites is present on the initial exploration, a sample should be sent for cytologic analysis before committing to resection [39]. Recurrences can be located centrally, in the pelvic side-wall, in the presacral plane or sacrum, or in the perineum. Central recurrences are localized to the pelvic organs and do not involve the bone or pelvic sidewall [42]. Tumors involving the pelvic side-wall are associated with the worst prognosis and least likelihood of attaining an R0 resection [50]. These recurrences may involve the ureters, iliac vessels, the greater sciatic foramen or sciatic nerve, the piriformis muscle, or the gluteal region [50]. Extensive involvement of the lateral pelvic side-wall is a relative contraindication to resection [50].

Dissection begins at the pelvic brim with identification of the ureters and iliac vessels [51]. The ureters are looped and traced to the base of the bladder [50]. If the recurrence is localized to the perineum, a transperineal approach may be possible. If the recurrence in this area involves the distal sacrum, a posterior distal sacrectomy may be required [39]. Vascular control may be necessary for many of the more complex cases. Intra-operative management of the arterial inflow and venous outflow proceeds as follows. The lower aorta, inferior vena cava, iliac arteries and veins are circumferentially dissected and controlled with vessel loops for proximal and distal control [42, 50]. Both internal iliac veins can be ligated in an effort to achieve an R0 resection [50]. The branches of the internal iliac vein are ligated and divided before ligation of the main trunk to avoid venous distension of the branches, which can lead to troublesome bleeding [42]. The internal iliac artery can also be ligated distal to the origin of the posterior branch which divides into the iliolumbar, superior gluteal, lateral sacral and variably inferior gluteal arteries [50, 52] . Preserving this first branch will maintain perfusion to the perineum and gluteal flaps should they be used for reconstruction and will also minimize wound related complications [42, 50].

Mobilization of the involved structures begins outside of the prior plane of dissection as this area may be unaffected by disease or extensive post-radiation changes [39]. Mobilizing the rectum for example, may be easier anterior to Denonvillier's fascia [50]. The type of resection performed for the primary disease impacts the plan for resecting the recurrence. If the primary tumor was in the proximal rectum and the anastomosis is higher in the pelvis, a low coloanal anastomosis may be constructed to maintain intestinal continuity after resection of a local recurrence. Alternatively, an abdominoperineal resection (APR) or an ultra-low Hartmann's with an end colostomy will be needed [50] if the prior anastomosis was low in the pelvis. Treating a recurrence following APR must take into account that the small bowel tends to fill the pelvis and may need to be resected *en bloc* with the recurrence [39, 50].

En bloc resection of all involved urogenital organs is recommended. If the recurrence involves only the dome of the bladder, a partial cystectomy can be performed [39, 50]. However, more extensive involvement of the prostate or bladder trigone in

men will necessitate rectal resection with prostatectomy (anterior exenteration), with urinary diversion [39, 53]. In an irradiated field, it may be difficult to determine if the prostate is involved with tumor or if scar and fibrosis from radiation are obscuring tissue planes. If the seminal vesicles are involved but the prostate is spared, these can be resected [54]. In women, invasion of the uterus or vagina may require hysterectomy combined with partial or complete vaginectomy [39, 50].

In cases where the radial margin is macroscopically close or the tumor involves vessels that are not amenable to resection, intraoperative radiation therapy (IORT) can be used. The radiation can be delivered using brachytherapy seeds or a linear accelerator. These methods eradicate microscopic tumor cells in the vicinity of the surgical margin and avoid exposure and collateral damage to the small bowel, ureter and bladder [39]. IORT requires specialized equipment for patient positioning and delivery of radiation and the collaboration of Radiation Oncologists trained in these techniques [39].

After the specimen is completely mobilized, attention is turned to the reconstruction. The splenic flexure and left colon are mobilized to allow for construction of an end colostomy [39, 42]. If a cystectomy has been performed, an ileal conduit is constructed for use as a neobladder [39]. The stomas are constructed and the abdomen is closed. A variety of options for reconstruction can be tailored to the patient's anatomy. An omental flap can be used to fill the pelvis after an APR to prevent the small bowel from adhering to the pelvis and prevent perineal wound breakdown [39]. Following an APR, a muscle-only gracilis flap can be used to fill dead space. In contrast to the vertical rectus abdominus (VRAM) flap, our experience with the gracilis flap resulted in good outcomes with the potential for less severe donor site complications, (most commonly minor wound dehiscence in 15%) and preservation of the rectus abdominus muscles for stoma placement [55]. The VRAM can be used for larger defects [39, 42]. The right side may be preferred if a colostomy will be placed on the left [50]. In a series of 100 patients undergoing transpelvic VRAM flaps for reconstruction after pelvic exenteration for anorectal cancer, major donor site complications occurred in 6% and VRAM-specific perineal wound complications were evident in 11% [56]. The disadvantages of the VRAM flap include a 13% risk of incisional hernia and imposed challenge of stoma location especially in patients requiring urostomy and colostomy [57]. Other considerations include avoiding gluteal flaps if they were in the radiation field and using rectus abdominus flaps if the internal iliac artery was ligated where a gluteal flap may be compromised [50].

Sacral recurrences are defined as tumor that is present in the presacral space and invades the sacrum [50]. Distal sacral involvement can be managed with a distal sacrectomy. More proximal involvement of S2 and S3 would require a high sacral resection which is associated with high morbidity related to motor and sensory neuropathies, bladder denervation and major pelvic bony instability [50, 52]. Surgical resection of sacral recurrences are managed in a combined abdominosacral procedure. Anteriorly, the dissection proceeds as outlined above, with identification and control of the ureters and iliac vessels. Special attention is paid to branches of the sacral veins. The lateral and middle sacral vein branches, which

drain posteriorly into the left common iliac vein and caval confluence, are ligated and divided [42]. The dissection is continued along the sacrum and onto the pelvic floor [42]. The anterior portion of the sacrectomy is aided by using intraoperative fluoroscopy to determine the level of transection and perform the anterior osteotomies [42]. A unicortical transverse osteotomy is made and marked with a small screw for fluoroscopic localization later in the procedure [42]. A thick piece of Silastic mesh can be placed against the sacrum and posterior to the vessels to protect the vessels and other soft tissue structures from the posterior blind osteotomy [42]. The ostomies are then matured and the abdomen closed. Then the patient is positioned prone and sacrectomy is performed with *en bloc* resection of the mass [39]. The second stage of the operation can be delayed 2–3 days if the patient has poor procedural tolerance [51].

The posterior portion of the procedure begins with a posterior midline incision from L5 down to the anus [50]. The gluteal muscles are reflected laterally away from their sacral attachments and the sacrospinous and sacrotuberous ligaments are divided opening up the presacral space [42, 50]. Once exposed, the piriformis muscle is divided while protecting the sciatic and pudendal nerves [42]. Fluoroscopy is used to identify the previously placed screw to guide the posterior osteotomy [50]. Laminectomy, dural sac ligation and sacral resection are then carried out [42]. Pelvic reconstruction follows.

R0 Versus R1/2 Resection, Outcomes

Radical surgery with curative intent for recurrent rectal cancer unsurprisingly has better outcomes than palliation [2, 5, 49, 58]. An R0 resection confers a 37.6 month survival benefit compared with an R1 resection and 53 months longer when compared with an R2 resection [59]. Surgery with curative intent can be performed safely with good outcomes. In a population-based study of 141 patients with locally recurrent rectal cancer, 25 (18%), were able to have surgery with curative intent. The resulting 5-year survival for these patients was 57% compared with 8.2% in those treated with palliation. Median survival was also much better for those able to undergo a potentially curative operation, 21 months *vs.* only 12 months for those treated with palliative chemotherapy or radiation therapy. Seven of the 25 patients experienced local re-recurrence, 4 of whom had concurrent distant metastases [4]. In a study of 153 patients by Heriot et al., 61% of patients with locally recurrent rectal cancer were able to undergo an R0 resection. Median overall survival was 43 months [60]. However, re-recurrence rates can be as high as 52% after R0 resection [61]. The benefit of an R0 resection was further demonstrated by Bhangu et al., who reported that 3-year local recurrence-free survival was 87% for those undergoing an R0 resection vs. 0% for an R1 or R2 resection [59]. More specifically, a tumor-free margin of ≥2 mm has been associated with better 5-year local re-recurrence-free survival than tumor-free margins of <2 mm (80% *vs.* 62%; P = 0.03) and better 5-year overall survival (60% *vs.* 37%, P = 0.01) [62]. Re-recurrence is more often systemic than local. The majority of treatment failures in a prospective study

of 533 patients undergoing pelvic exenteration for recurrent rectal cancer were systemic, with 56% of patients experiencing systemic failures and 26% having both systemic and local failure [63].

Dozois et al. reported outcomes for 9 patients undergoing high sacrectomy for recurrent rectal cancer. Only one of 9 patients experienced local re-recurrence. Median overall survival was 31 months with 30% 5-year survival. All deaths were due to metastatic disease. Major complications were mostly related to wound dehiscence but also included a missed enterotomy and re-operation for bleeding. When bilateral S2 nerve roots were sacrificed, urinary retention was universal [42]. A later series from the Mayo Clinic evaluating 30 patients undergoing extended sacropelvic resection for recurrent rectal cancer up to the fourth lumbar space demonstrated a 46% 5-year overall survival with only 40% major morbidity [51].

Chemoradiation

Chemoradiation is a part of multi-modality treatment for recurrent rectal cancer. However, recurrent rectal cancer may not respond as favorably to chemoradiation as well as the primary tumor. In a study comparing patients with primary rectal cancer to previously chemoradiation-naive patients with recurrent rectal cancer who were all undergoing preoperative chemoradiation, those with primary rectal cancer were 2.4 times more likely to have >50% reduction in tumor size than patients with recurrent rectal cancer. The results also suggested that only patients who experienced a 50% reduction in tumor size had a benefit in 3-year overall survival [64].

Pre-operative chemoradiotherapy may increase resectability and the chance to achieve an R0 resection from 26% to 43–50% [65]. A study of 35 previously non-irradiated patients with pelvic recurrence of rectal cancer involving contiguous organs found that a combination of high-dose preoperative chemoradiotherapy followed by extended surgery can achieve clear resection margins in more than 60% of patients with recurrent rectal tumor not amenable to primary surgery [66]. The combined effect of pre-operative chemoradiation in radiation-naïve patients with recurrent rectal cancer and an R0 resection can increase 3-year local progression-free survival by 20% [67]. A multicenter phase II study to evaluate the outcomes of preoperative hyperfractionated chemoradiation for isolated locally recurrent rectal cancer in patients with prior pelvic irradiation found an overall median survival of 42 months and 5-year OS of 39.3%. This study again demonstrated the importance of attaining an R0 resection. Five-year OS in R0 resected patients was 66.8% compared with 22.3% in those treated without surgery or undergoing either R1 or R2 resection. With respect to palliation of symptoms, 83.3% of those presenting with pelvic pain had a symptomatic response [5].

Radiation for recurrent rectal cancer may be more effective in patients who did not receive adjuvant treatment for their primary malignancy rather than in patients undergoing repeat treatment. In a pooled analysis of 565 patients undergoing multimodality treatment containing intraoperative radiation therapy (IORT) for locally recurrent rectal cancer, 5-year re-recurrence rates were significantly lower in

patients receiving full preoperative chemoradiation therapy for their recurrence (38%), and higher in patients not receiving any preoperative therapy (52%), or repeated chemoradiation (58%) [65].

IORT is a useful tool when dose escalation beyond EBRT tolerance limits is required for local control in recurrent rectal cancer. Previously irradiated patients may be carefully re-treated with radiation and IORT in addition to chemotherapy resulting in long term survival [68]. IORT can be delivered via linear acceleration-based electron beam radiation therapy (EBRT) or with brachytherapy. IORT can be followed with post-operative EBRT. While R0 resection remains the most important predictor of local control, the addition of IORT and EBRT confers a survival benefit [69]. Recurrences following IORT tend to be distant metastases [70]. Intraoperative brachytherapy can be used when narrow pelvic anatomy is unfavorable to EBRT and has the added advantage of decreasing the incidence of neuropathy [69].

Conclusions

Successful treatment of recurrent rectal cancer involves identifying patients at high risk for recurrence based on margin positivity, distal location, poor histology, and poor quality of initial TME. Successful management requires a systematic approach to diagnostic evaluation focusing on the potential to obtain an R0 resection with the implementation of multimodal treatment which includes neoadjuvant chemoradiotherapy, intraoperative radiotherapy, and radical resection. Of the multiple risk factors associated with a local and regional recurrence of rectal cancer, we believe that a positive margin after the first operation is the single most important factor. What is surprising is that only 40% recur with a positive margin instead of an anticipated 100%. A distal location for anatomic reasons leads to a higher rate of recurrence. The margins at the initial surgery for distal rectal cancers are frequently closer. One reason for this is that mesorectum is narrower in the distal rectum below Waldeyer's fascia. The quality of the mesorectal dissection at the initial surgery is also an important risk factor. Surgeons without specialty training in colorectal surgery, fewer years of experience, and lower operative volume are more likely to have more recurrences, perhaps due to a higher rate of inadequate TME. Secondly, the tumor can spread outside the mesorectal fascia to the lateral pelvic lymph nodes instead of staying confined to the mesorectum. Finally, one of the reasons local excision recurrence rates may be higher than radical resection is that most local excisions are performed on distal rectal cancers, while the results after radical resection will include patients with distal, mid- and proximal rectal cancers. One can predict by location alone that recurrence would be less in the radical resection group. The third most important factor determining recurrence is histology, although it is not clear whether this is an independent risk factor or one that leads to a higher rate of positive lymph nodes or a higher positive margin rate. Poor histology may be more of a factor in distant recurrence.

The diagnostic and treatment algorithm begins with a PET-CT to rule out distant recurrence. If this is negative, MRI of the pelvis can be performed to assess resectability. Neoadjuvant chemoradiotherapy should be considered with the addition of intraoperative radiotherapy if possible. Our institutional preference is that brachytherapy can be administered if there is difficult pelvic anatomy. Reconstruction with vascularized tissue flaps may be a useful adjunct. Outcomes are improved with the use of a multi-disciplinary approach.

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Chapter 29
The Management of Recurrent Rectal Cancer: An Australasian Perspective

Jacob McCormick and Frank A. Frizelle

Introduction

The management of rectal cancer has evolved considerably over the last 30 years. Improvements have focused greatly on the goal of reducing the risk of local recurrence which, unfortunately still occurs, albeit less frequently. Since the introduction of total mesorectal excision (TME) and a more standardized approach towards preoperative chemotherapy and radiation, clinical trials have held local recurrence at the forefront of treatment outcome measures. In this respect, the goal of reducing local recurrences has largely been achieved with local recurrence rates generally falling in reporting centres from rates of 18 to 30% down to between 3 and 8% [1–4].

Despite these measures, isolated local recurrences does still occur and for those patients with local pelvic recurrence, death can be a painful process with in some cases, the unpleasant prospect of the slow development of a malodorous, fungating, fistulating perineal mass [5, 6]. For a number of patients with isolated local recurrence there remains the possibility of further more radical surgery, where excision of the pelvic recurrence with curative intent remains a treatment option. The extensive nature of the surgery required to obtain clear resection margins is morbid and requires careful patient selection based upon the definition of the extent of the disease, the assessment of the patient physiology and an evaluation of psychological parameters which may influence the adaptation to extensive surgery. The development of spe-

J. McCormick · F. A. Frizelle (✉)
Christchurch Hospital and University Department of Surgery, University of Otago, Christchurch, New Zealand
e-mail: Frank.Frizelle@cdhb.health.nz

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cialized centers along with multidisciplinary cancer management teams and associated improvements in perioperative management and intervention have now seen extended radical resection become the standard of care.

Incidence

Most primary rectal cancers are now removed by major abdominal surgery using a technique that follows the fascial plane investing both the rectum and the mesorectum (total mesorectal excision -TME) [5] with the technique reducing local recurrence rates down to between 3 and 8%. This can be compared with older historical, traditional techniques which cone down into the mesorectum close to the rectal wall and which do not respect its surrounding fascia or its embryological development, resulting in local recurrence rates of 20–40% [1, 2]. Current data suggest that up to 5–10% of patients who undergo resection of a rectal cancer will develop a local recurrence [7]. At least 50% of patients who develop local recurrence will also have distant metastatic disease and as such will not usually be suitable for radical surgery. For patients with isolated local recurrence, however, *en bloc* resection of involved structures offers the chance of cure. In a small subset of patients with local recurrence and distant disease, radical resection may offer useful palliation [8].

Patterns of Local Recurrences

The usual description used is based upon the anatomical location; namely as central, anterior, posterior and lateral (left and right) (Fig. 29.1). This general approach is used in the absence of a standard classification system for locally recurrent rectal cancer. Within each location there is a subdivision which is outlined in Table 29.1.

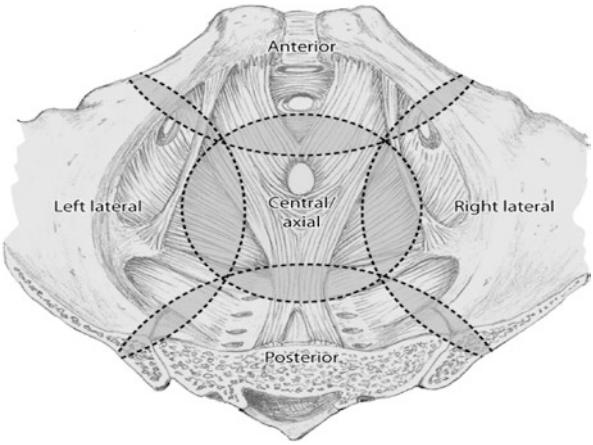

Fig. 29.1 Patterns of local recurrence

Table 29.1 Patterns of local recurrence

Site	Description
Central	High enough for anastomosis Needs APR
Lateral	Below bifurcation of anterior and posterior trunks of the internal iliac artery Above bifurcation of anterior and posterior trunks of the internal iliac artery
Anterior	*Female* Uterus *in situ* Previous hysterectomy Vagina only involved Bladder involved – above trigone Bladder involved – involving trigone *Male* Involving seminal vesicles only Involving prostate only Involving bladder; trigone spared Involving balder trigone involved
Posterior	Pelvic floor only Coccyx At or below S3 Involving S2 Involving S1

APR abdominoperineal resection

Table 29.2 Frequency of sites of recurrence from 533 patients in a multinational study [9]

Anterior compartment – 208
Posterior – 176
Lateral – 126
Central and pelvic brim – 90

This classification really emphasizes the surgical considerations of each site where recurrence can, (and with increasing frequency does), involve more than one site.

Table 29.2 shows a summary of local recurrence sites in a recently published multinational retrospective analysis [9]. This group had a 42.4% associated incidence of distant metastases with in 226 evaluable cases the majority in the liver (52 patients), the lungs (s) (75 patients), or other sites within the peritoneal cavity distant to the local pelvic recurrence (79 patients). For the purposes of definition: Central tumors are localized to the pelvic organ(s) and the adjacent soft tissues without any bony adherence. Sacral tumors involve the presacral space and may infiltrate the sacrum and/or coccyx. Lateral pelvic sidewall involvement infiltrates soft tissues and structures along the pelvic sidewall (iliac vessels, lateral pelvic lymph nodes, pelvic ureters, pelvic nerves and sidewall musculature – the piriformis and obturator internus) or the lateral bony pelvis.

Within the assessment of some of this data there are several caveats. Overall, anterior recurrences are rare except for cases where the primary tumor had initially been a Stage T4 [10]. The central and posterior recurrence patterns likely represent residual tumor within lymphatic channels and lymph nodes left behind within the

mesorectum (since the main bulk of the mesorectum lies in the posterior plane within the pelvis). Involvement of the sacrum is usually through local invasion but may also occur by haematogenous spread especially if S2 or S1 only is involved (Fig. 29.2). Lateral side wall recurrences in reports are often localized to the internal iliac lymph node chain. As well as these points, increasingly, patients are being seen who have multifocal disease in the pelvis (e.g. perianastomotic recurrence combined with pelvic side wall lymph node involvement).

Historically, the main pattern of local recurrence considered for repeat resection was the central recurrence within the pelvis and often posterior to the anastomosis [10]. In this event, there is often a significant buffer of residual mesorectum left between the recurrent disease and the vital structures such as the ureters, main vessels and the bony pelvis. This presentation is largely the result of performing an incomplete TME at the initial operation and resection of these cases tends to focus generally on the re-performance of what in effect amounts to a good quality repeat TME. With a better surgical understanding of the role of TME in reducing local recurrence these easier cases are now relatively rare [5, 10], however, they account for the most favourable prognosis with the highest potential chances of achieving a clear resection margin [6, 11, 12]. Since TME has become such a standard surgical procedure and the bulk of the rectal cancer resection workload has been taken on by colorectal surgeons there has been a shift in recurrence patterns over the last 20 years.

This change in recurrence pattern represents a new challenge for the surgeon managing recurrent rectal cancer as planes of dissection need to be entered that are not part of the usual rectal dissection. In addition, the buffer of residual mesorectal fat that previously protected the re-resection margin has been lost and multi-visceral resections are often required in order to achieve an adequate/R0 resection in these

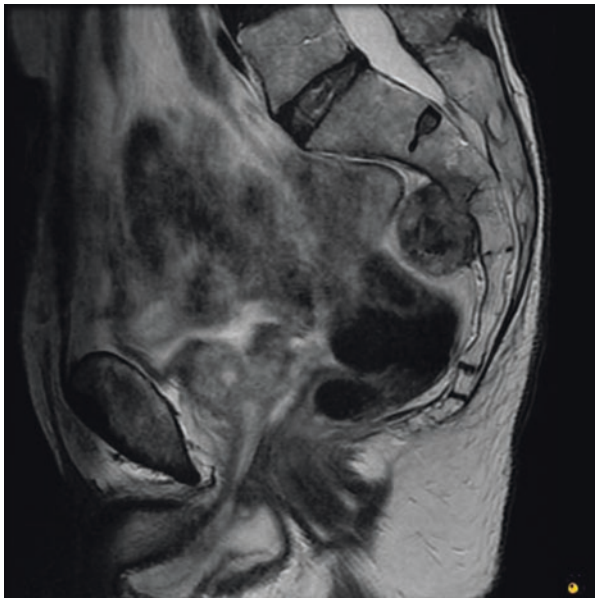

Fig. 29.2 An S2 metastasis

cases. In our opinion this has increased the level of difficulty for surgical management of recurrent rectal cancer and turned it into a true team-based exercise where the colorectal surgeon is required to manage the input of several specialties, particularly including urology, vascular and orthopedic services.

Risk Factors for Local Recurrence

Many risk factors for local recurrence have been identified over the years. Some of these are related directly to the tumor itself, such as the initial volume of disease and the degree of differentiation, and are thus are unable to be altered [13]. However, a significant proportion are directly related to decisions made in the management of the initial cancer episode. In this chapter, we focus on these remediable factors as an awareness will assist the treating clinician in substantially reducing their rates of local recurrence.

All local recurrence can be defined as occurring as a result of the interaction of two principal factors:

1. Patient factors e.g. advanced cancer, poor differentiation, a narrow pelvis, obesity, the desire for restorative surgery etc. and,
2. Management factors e.g. perioperative management, preoperative chemoradiation (use or absence, fields utilized, dose, fractionation), surgical technique etc.

As there is little a surgeon can do to influence patient-related factors we have concentrated on the management-related factors that are of clinical significance to the treating surgeon.

Circumferential Resection Margin (CRM)

Involvement of the CRM in the resected specimen has been shown to markedly increase the rate of locoregional recurrence –from 10 to 78% in one study reported by Heald and colleagues [2]. Involvement of the CRM independently influences both local recurrence and cancer-specific survival where this study showed that the CRM was involved in 25% (35/141) of cases in which the surgeon thought the surgery had been “curative” indicating that the clinical assessment at the time of surgery is inaccurate. High-quality pre-operative assessment of the primary rectal tumor, particularly with MRI (Fig. 29.3) has become fairly standard practice as it allows for the clear identification of patients who are at risk of an involved CRM [14]. This issue originally initiated by the MERCURY Group at the Royal Marsden Hospital in London is addressed in the imaging section of this book (Chap. 4). Following high resolution MR imaging a discussion can then be conducted regarding the merits of neo-adjuvant radiotherapy (with or without chemotherapy) in a selective effort to down-stage and down-size the tumor, sterilizing the operative field [15].

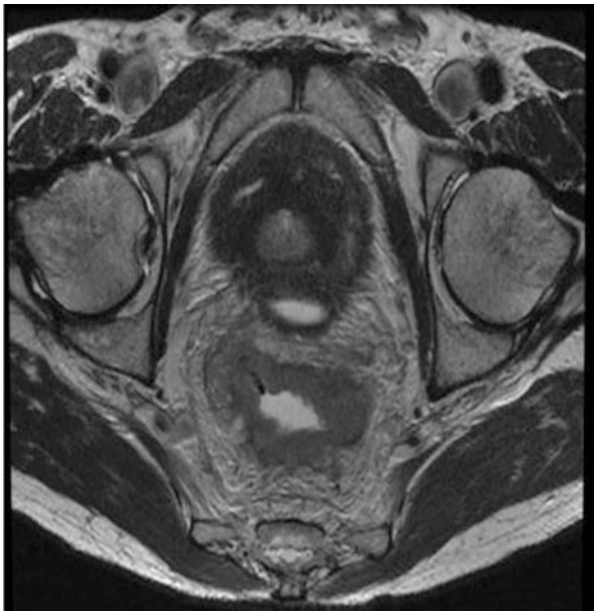

Fig. 29.3 MRI of pelvis showing rectal cancer invasion into mesorectum with intact CRM

Radiotherapy with or Without Chemotherapy

Upfront resection of rectal cancer and delaying the decision to give postoperative radiotherapy pending histopathology has been shown to be markedly less effective than preoperative radiation therapy. Early radiotherapy trials such as the "Swedish Trial" showed significant benefit to the provision of Short-Course Radiotherapy (5 Gy × 5 days) with specific regard to local recurrence (27% preoperative RT *vs* 11% no preoperative RT, respectively at 5 years) [16]. This issue is complicated, however, since the surgery performed over this period is likely to have been considered inadequate by today's TME-standard. By comparison, the Dutch TME trial (SCRT + TME *vs*. TME-alone) is most applicable to today's surgical standard and this definitively showed a reduction in local recurrence rates from 11 to 5% at 10 years by the addition of SCRT [4]. Further studies of long-course chemoradiation have shown similar reductions in the local recurrence rate with the added benefit of tumor down-staging and down-sizing prior to initial resection [17].

Patients whom we would normally consider for radiation therapy are outlined in Table 29.3. Tumors located in the distal third of the rectum are technically more challenging to resect than those situated in the middle and upper thirds due to the anatomical confines of the pelvis. Moreover, the mesorectum tapers distally such that there is much less of a buffer of mesorectal fat at these points which surrounds the tumor and its adjacent lymph nodes. Anteriorly-based distal tumors are particularly at risk as there is often very little margin between the tumor and the posterior vaginal wall in females or the prostatic capsule in males.

Table 29.3 Recommended patient categories of benefit from preoperative chemoradiation

Variable	Consider preoperative radiotherapy (+/− chemotherapy)
CRM	Positive
T stage	T3 T4
N stage	N1
Height above the anus	Rectum as defined by MRI findings not rigid or flexible sigmoidoscopy
Site	Anterior in males
Operation	Need for APR for clearance

Our unit would consider long-course chemoradiation for any one of the following;

- Patients with a threatened (<2 mm) or a frankly involved CRM on clinical staging
- Patients with a T4 tumour
- Males with an anteriorly-based tumor abutting the prostate (due to the lack of mesorectum)
- Those patients who require an APR for clearance (due to the high positive margin rate with APR's) [18].

Although the latter indication may be considered controversial, these recommendations are based on a recently reported risk of CRMs retrospectively assessed by multiple collaborators (the Consortium for Optimizing the Treatment of Rectal Cancer – OSTRiCH) which showed that there was a greater chance of CRM involvement in 16,619 cases analyzed where CRMs were involved in 17.2% (2859 cases) with: clinical T and N stage, histologic type, tumor size and grade, lymphovascular and perineural invasion and specifically with total proctectomy (APR or pelvic exenteration). The latter procedure had an OR of 1.293 of CRM involvement over partial proctectomy (95% CI 1.185–1.411) with laparoscopic surgery reducing the odds of a positive CRM in this series by some 22% overall [18].

Our group would consider short-course radiotherapy for T3 and N1 cancers not meeting any of the above criteria. The role of preoperative short-course radiotherapy alone versus long-course chemoradiation is still being defined [4, 19, 20]. Short-course RT if shown to be equivalent will have significant resource-management benefits [21, 22] as well as an impact on treatment-related adverse events [23], patient convenience, overall costs and health-related quality of life considerations [24]. The impact of these decisions will be felt regionally; for example, long-course therapies are still favoured in the United States [25] despite several trials failing to show benefit [26, 27].

Obesity

Obesity is a modern day epidemic and makes the management of rectal cancer in some cases very difficult on multiple levels. Some patients are too large for conventional MRI scanners and standard ward beds, operative (including laparoscopic) equipment and for regular operating tables. The surgery is technically challenging

due to the effort required to retract soft-tissues and organs, the added depth to the pelvis and the fragile nature of the additional intra-abdominal fat. The accumulated difficulties result in higher rates of local recurrence. In our morbidly obese patients we would generally give them all long-course chemoradiation. We do not find them easier to operate upon laparoscopically and prefer to undertake an open operation. In this regard, we position the patient tilted to 45 degrees with the left side up to allow the small bowel to fall out of the way and to try and avoid any stoma by using a hand sewn intra-anal anastomosis [28–30].

Laparoscopy vs. *Robot* vs. *Open Resection*

Laparoscopic resection of colon cancers has been shown in non-inferiority designed trials to be of equivalent oncological benefit to open surgery [31–33]. Recent similarly-designed laparoscopic trials evaluating rectal cancer resections appear to show similar results for rectal cancers specifically in the upper two-thirds of the rectum [34, 35]. Rectal cancers in the lower one third of the rectum, however, may not be as effectively managed by laparoscopic surgery. The recently presented ALaCart trial from Australia and New Zealand which is still maturing has shown some concerning results for distal third rectal cancers where there are more positive margins [34]. In this trial, amongst T1–T3 rectal tumors overall, noninferiority of laparoscopic surgery when compared with open surgery was not established and as in both cohorts the quality of surgery was high, the case for routine laparoscopic resection was not made. The ROLARR trial, a randomized, controlled superiority trial of robotic-assisted versus standard laparoscopic surgery for the curative treatment of rectal cancer has likewise raised concerns about the distal third cancers [36]. The result of these concerns has encouraged surgeons to consider undertaking the lower third mesorectal dissection transanally [37], an issue the technical details of which are discussed in Chap. 10 of Part IV by Professor Lacy. The oncological significance and impact of such change in practice is still uncertain and in our view trans-anal TME (TaTME) currently requires a rigorous assessment via a well-designed clinical trial to determine its surgical place.

Post-operative Surveillance After Primary Rectal Cancer Surgery

There are three main aims to surgical follow-up. These include (1) an ability to allow the acquisition of prognostic information for patient reassurance, (2) to facilitate audit of the clinical effectiveness of treatment and (3) to allow for the identification of recurrent disease and its definitive management.

For surgical units which perform surgery on those select patients with recurrent rectal cancer, the principal interest is in identifying disease recurrence (local or

distant) at a stage that an intervention could be performed and which may alter the natural history of disease. The identification of recurrent disease may prove particularly difficult. Large recurrent lesions are often easier to identify, however, the prospects of performing successful surgery in this setting are often limited. The great challenge is in identifying recurrent disease at a stage early enough which will permit successful surgery and in delineating between the early signs of recurrence and non-malignant post-operative (post-inflammatory) changes where re-resection is contraindicated.

Follow-up protocols need to be tailored to the local health-care environment taking into consideration time, access to specialized investigation and multidisciplinary care, the expertise and sensitivity/specificity profile concerning investigative interpretation, the likelihood of identifying recurrent disease, the ability to treat recurrent disease (surgical and patient-factors) and overall costs.

Our routine follow-up is protocol-driven and involves a combination of clinical examination, serial CEA levels, cross-sectional imaging and endoscopy. A rising CEA level, whilst not specific for CRC raises suspicion in a patient who has had a rectal cancer and this will trigger further investigations as required [38]. Newer imaging modalities such as CT-PET (Fig. 29.4) and the higher-resolution images we can obtain from modern CT and MRI allow for the identification of recurrent disease which is potentially resectable and these modalities make it easier to separate true recurrence from postoperative scarring at an earlier stage [39]. The role of PET CT scanning in rectal cancer and controversies in its use are discussed in Chap. 4.

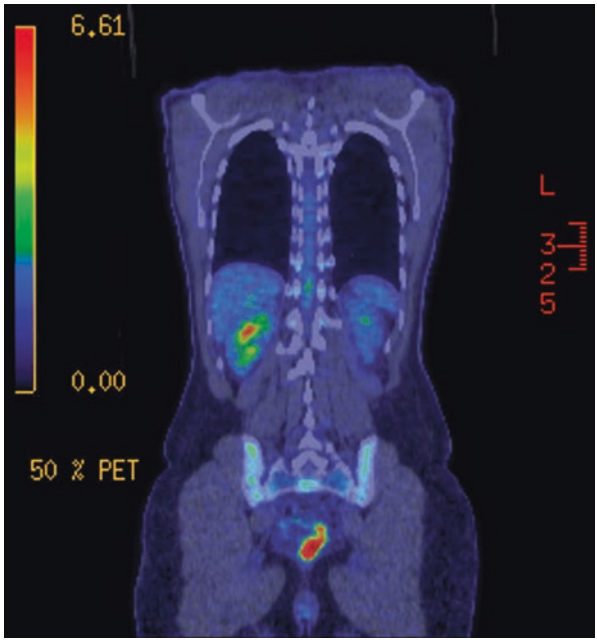

Fig. 29.4 FDG PET-CT scanning showing a locally recurrent rectal cancer with liver metastasis

Preoperative Assessment of Recurrent Rectal Cancer

There are four factors that we believe are important in the preoperative assessment of patients identified with local recurrence.

Patient Education About the Choices

Radical pelvic surgery has a significant impact on a patient's immediate quality of life [40]. The tradeoff between potential longer survival or improved palliation and immediate quality of life is a very important issue to discuss in depth and often repeatedly with patients and their family. Surgeons can at times have an overly optimistic view of the outcome and likewise patients can at times focus more on survival at the expense of quality of life. This potential distortion of perspective can lead to inappropriate surgery and poor patient outcomes. Empathetic education about what the surgery means and alternatives available are an essential part of counseling designed to maximize patient wellbeing.

Determine the Fitness of the Patients for Surgery

Surgery for recurrent rectal cancer is a major undertaking that induces both a severe physiological and psychological stress. The anesthetic assessment may be prolonged and input from a cardiologist, respiratory or renal physician may at times be required. Whilst not routine, we will often use cardiorespiratory stress testing preoperatively when we are uncertain about fitness for an operation.

Localization of the Rectal Cancer

This is used to determine the appropriateness and goal of surgery (palliation *vs.* cure). We would routinely arrange for CT scans of the chest, abdomen and pelvis as part of the assessment of recurrence. We do not usually biopsy suspected recurrences and if done prior to referral we would excise the biopsy tract. We would also perform PET-CT in all patients prior to resection in order to identify occult distant disease and so as to exclude those patients where radical extirpative surgery would be futile.

Assessment of Local Anatomy

This is for the planning of the details of the operation and not the determination of whether an operation is appropriate. Our standard practice is to perform a pelvic MRI as we find this provides good delineation of the recurrence relative to soft

tissue, bony and vascular margins. At times this may also involve a CT-Angiogram with 3D reconstruction definitively assessing the arterial and venous anatomy.

Preoperative Treatment

Preoperative chemoradiation, if not used in the primary cancer is of benefit prior to re-resection [8]. If the patient has had some initial radiotherapy, a review of the total dose and fractionation by an experienced radiation oncologist may allow further radiotherapy to be administered. Special consideration needs to be given to toxicity in these patients as they will often have small bowel in their pelvis from their previous procedure. On occasion there may be a selected role for chemotherapy, especially in the chemotherapy-naive patients, or those who have only been exposed to single agent chemotherapy [8].

Surgery: General Principles

Resection of pelvic recurrences should be targeted to the individual pathology. The location of the recurrent disease dictates what procedure should be performed. Despite the advances in pre-operative imaging currently available the final decision of what needs to be resected is often only apparent at the time of surgery with the goal of achieving an R0 resection.

We favor a team approach with a regular anesthetist and a small pool of urological, vascular, plastic, gynecological and orthopedic surgeons whom we work with for these procedures on a regular basis. Despite their regular involvement in these cases and unique skill-sets we remain directly involved in the resection as it is the role of the co-ordinating colorectal surgeon to ensure adequate resection margins are taken.

Exenterative procedures are often long procedures and frequently require an extended operating list session. Whilst clear margins are the main goal, care must be taken not to waste time with unnecessary maneuvers and in this regard, we aim to rotate key members of the operating team through regular breaks in order that they remain fresh for the part of the procedure concerning their surgical responsibilities.

Often there is a very fine line between what is resectable and what is unresectable. It must also be noted that up to 5% of patients with a local recurrence will also have metastatic disease found at operation despite an extensive preoperative workup [41]. It is possible that this distant disease may have developed between the decision to perform the exenteration and the operation date, particularly if time has been taken with additional radiotherapy. Our patients are admitted several days prior to their surgery and are completely re-staged within 48 h of their operation with CT scans of their Chest/Abdomen/Pelvis and MRI of their local disease in order to obviate this problem. These images are reviewed the day before surgery with a radiologist in our multidisciplinary team meeting. New or suspicious dis-

ease such that the exenteration would not be of curative intent will result in cancellation of the procedure.

Many patients will require ICU post-operatively. This being a combination of the size of the operation and the age/co-morbidities of the patient. A commitment from the ICU the day prior to the procedure that they will have a post-operative bed, should it be required, is ideal as this allows for an on-time start to the operating list and avoids late-night finishes.

If the disease appears to be close to the ureters on imaging, we will routinely place ureteric catheters. Ureteric catheters may not prevent injury but they aid in identifying injury intra-operatively should it occur so that this aspect may be addressed during the initial procedure [42, 43]. This helps to avoid an unrecognized injury presenting as a postoperative urine leak which is much harder to manage. An inability to pass a ureteric catheter is often indicative of ureteric involvement and the subsequent need for resection. A retrograde pyelogram is unnecessary in this setting and just adds additional time in our opinion without benefit to an already long procedure.

We begin with a diagnostic laparotomy to search for any distant or peritoneal disease that may not have been identified pre-operatively. The presence of further metastatic disease will often change the treatment goal and in this setting we may opt for a smaller, palliative procedure with a shorter recovery period.

Many patients will have had a stoma with their previous surgery. Care is taken at re-operation to preserve the inferior epigastric vessels as a vertical rectus abdominis myocutaneous (VRAM) flap may be necessary for perineal reconstruction after an exenterative procedure. Consequently we would often place an end colostomy on the right side if there had previously been a loop ileostomy there and we wished to use the left rectus abdominis muscle and/or the adjacent skin paddle for a VRAM flap.

A thorough adhesiolysis is often required just to obtain access to the pelvic recurrence. A good three-dimensional understanding of the pelvic structures, particularly the iliac vessels and ureters is important in this dissection, correlating these structures with the preoperative imaging in order to identify the location of the recurrent disease in what is usually a very scarred field. Intra-operative reference to the imaging is particularly important with lateral pelvic sidewall recurrences so as to locate the level of disease and in this respect, the iliac bifurcation is a handy reference point.

It cannot be stated enough that the key to operating on recurrent rectal cancer is achieving an R0 resection. This will require *en bloc* resection of the recurrent disease and any adherent/adjacent organs, referred to as Extended Radical Resection. The location of the disease largely determines the organs removed and the surgical teams involved. Small bowel is often involved, as is the uterus and ovaries in females although a uterus that has "flopped backwards" following the initial resection often acts as a barrier to involvement of other organs.

As a general principle, posterior recurrences often require a partial sacrectomy. Lateral recurrences may require resection of the ureter +/− the iliac vessels with resulting reconstruction. The previous anastomosis may need to be taken down and converted either to a coloanal or an APR depending upon the level of the recurrence and the locale.

Anastomotic Recurrence

Anastomotic recurrence (AR) usually represents a failure to obtain an adequate margin at the first operation. This may be evident endoluminally and depending upon the level it is often appropriate in this setting to resect the anastomosis and perform a sphincter-saving operation (provided adequate distal margins are achievable). If the recurrence is to one side or the other, particularly after a high-anterior resection then this may require the *en bloc* resection of a distal ureter. If this is just on the one side it is usually possible to perform a direct ureteric-bladder anastomosis (neoureterocystostomy) of one's choosing. While in some of these patients it is possible to restore intestinal continuity often the function is poor (impairing quality of life) due to multiple pelvic dissections and irradiation.

Posterior Recurrence

Posterior recurrences represent tumor within the residual mesorectum. It is usually harder to perform a restorative operation in this setting so conversion to an APR (+/− coccygectomy/sacrectomy) is often required. Pre-operative local staging provides a good indication of whether the standard TME plane is threatened. Should the standard TME plane be threatened then the presacral tissue may be incised superior to the tumor and the dissection continued posterior to this up hard against the sacrum. If this technique is employed then careful attention must be given to controlling the presacral venous plexus as bleeding here may be significant and should be expected as part of the need to resect some of the rectosacral fascial layer of Waldeyer. Should the tumor directly extent to the sacrum then a sacrectomy will be required despite its attendant significant morbidity. Not unexpectedly, the postoperative complication rate and median length of hospital stay following sacrectomy decreases the more distal the sacral resection [44].

Anterior Recurrence

There is very little mesorectum anteriorly. Recurrence here is a result of shedding of tumor cells and/or inadequate margins at the initial operation. There may be direct invasion of the bladder, uterus, vagina or prostate, giving some protection to more-critical structures. Invasion can be estimated on preoperative imaging, but it is extremely difficult to definitely assess this feature until all is viewed histologically. The previous dissection makes it difficult to distinguish between recurrent disease and normal postoperative scarring both on imaging and at re-resection. *En bloc* resection of structures suspected of being involved, or necessary to achieve an adequate margin is required. This may require cystectomy with ileal conduit or vaginectomy with or without reconstruction. In females who have not previously had a

hysterectomy the uterus provides a buffer of protection to the bladder and in this setting *en bloc* hysterectomy may be all that is required.

Perineal Wound Recurrence (Post-APR)

We do not seem to see this type of isolated presentation very often and when we do it is often seen as part of a wider failure. Where wide local excision can be achieved this is often definitive for local control. There is, however, a high-likelihood that this is the "tip of the iceberg" given that the pelvic space was opened up at the previous operation. Where this is part of a larger intra-pelvic mass we would favour an abdominal approach to remove small-bowel from the pelvis and prove that there is no enteric involvement. We would then proceed to take further lateral and posterior margins *en-bloc* with re-excision of the perineal scar and VRAM reconstruction flaps for closure with a cylindrical pelvic floor excision as per an extended (Extra-levator –ELAPE) style APR.

Lateral Recurrence

Involvement of the lateral pelvic sidewall is the most challenging of these operations, however, with the aid of a vascular surgeon considerable benefit can be gained by sidewall clearance and at times the rectum can be preserved by mobilization, distracting it medially and taking care not to disrupt the previous anastomosis or the blood supply. Dissection may require selective vascular ligation of the internal iliac tributaries with partial removal of the obturator internus muscle and sacrifice of the obturator nerve but with preservation of the lumbosacral trunk [45, 46].

To Leave the Bladder or Take the Bladder?

Removal of the urinary bladder will require some form of urinary diversion, most commonly now in the form of an ileal conduit. The creation of an ileal conduit usually adds three anastomoses (small bowel to small bowel; small bowel (conduit) and ureter ×2), plus the need for a further stoma site on a side where the rectus muscle (with or without skin) may have been harvested to construct a VRAM flap. We believe this adds a not inconsiderable morbidity to the procedure and it may be further compromised by the need for synthetic or biologic mesh insertion for abdominal wall reconstruction in some cases. If at all possible, we aim to preserve the bladder. Obviously there are situations where this is not possible, as for example when there is direct involvement of the trigone or both distal ureters. Many

institutions still take the bladder when removing the prostate *en bloc* with a pelvic recurrence. Our group has shown that this is not universally required and we will often disconnect the bladder from the urethra, leaving the prostate on the recurrence and performing a urethra-to-bladder-neck anastomosis with good results even in irradiated tissue [47]. In this group, overall survival is comparable to that obtained with a conventional radical cystoprostatectomy and urinary function is acceptable (urinary continence in 36% and mild incontinence in 27%) without the need for a conduit or double stoma.

To VRAM or Not to VRAM?

There are a number of flaps which can be used when tissue is required. We have preferred the VRAM flap, as it has been out of the radiation field, can contain a skin paddle if required and is robust and reliable [48]. This approach requires considerable planning and also permits potential vaginal reconstruction in selected cases. Its results appear to have less morbidity than primary reconstruction particularly in the heavily irradiated case [49]. The use of the VRAM flap is not always convenient, however, especially after a sacrectomy when the patient has been in prone jack knife position where other reconstructive options such as the lotus flap may be considered [50].

MDT Discussion

Guidelines in Australia and New Zealand recommend multi disciplinary team discussion for all primary and recurrent rectal cancers [51, 52]. Though the evidence of benefit for this is limited, there appears to be value in bringing together surgeons, medical and radiation oncologists, radiologists and pathologists as well as specialist practice nursing staff and the various ancillary service providers (such as enterostomal therapists) so as to determine the optimum treatment plan with input from the various specialist sectors [53].

Outcomes

Most data on outcome has been limited to single specialist centers raising questions concerning data reproducibility. Multicenter data on outcomes has been slow. A recent international multicenter study of 533 patients who had undergone surgery for locally recurrent rectal cancer found that the all-cause mortality in the study population was a 28% survival at 5 years [9]. Analysis of cancer-specific mortality

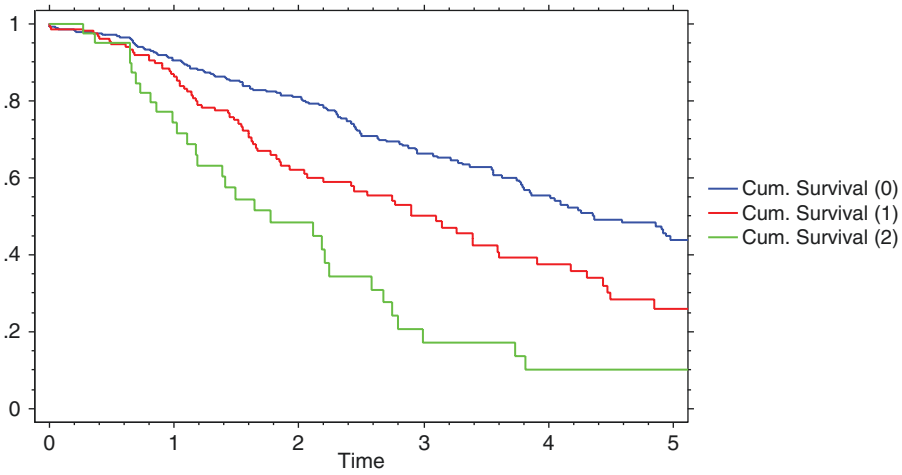

Fig. 29.5 Cancer specific death: Effect of R stage (R0 *vs.* R1 *vs.* R2). Logrank (Mantel-Cox). Chi-Square 48.050, DF 2, P < 0·0001

demonstrated in this study a 37% survival at 5 years. The 5-year survival for patients with a complete (R0) resection is 44% (Fig. 29.5) and, in this event, R0 resection was achieved in 59% of patients. Radical resection required a sacrectomy in 170 patients (32%) and a total cystectomy in 105 patients (20%). Treatment failure included local recurrence alone in 75 patients (14%) and systemic metastases with or without local recurrence in 226 patients (42%) (Table 29.2).

Summary

Recurrent rectal cancer is best managed by avoiding the problem in the first place. That said, there will always be some patients who develop recurrent rectal cancer and the different patterns of pelvic recurrence govern the opportunity to completely re-resect disease where an R0 resection is the only potential guarantee of cure. The surgeon needs to be realistic about what can be achieved with the aim of focusing on improving the patient's quality of life with attendant local tumor control. With improvements in the quality of the initial management and surgery, the recurrences that are referred to specialist centers appear to be harder to deal with and more likely require extended resections. Careful preoperative patient education and planning with a multidisciplinary team with a focus on assessment of patient fitness along with high quality staging using CT-PET and MRI allows the selection of patients where surgery is not futile and which may prove of benefit. In order to obtain the best results surgery should be conducted under the auspices of a multidisciplinary team with the requisite experience and volume of cases handling rectal cancer patients.

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Part IX
Uncommon Rectal Tumors

Chapter 30
Managing Uncommon Rectal Tumors

Erica B. Sneider and Justin A. Maykel

Rectal adenocarcinoma is a relatively common malignancy and it is estimated that there will be 40,000 new cases diagnosed in the United States alone in 2017 [1]. Whilst adenocarcinoma is the most common malignancy of the rectum, other rectal tumors can occur including most commonly, carcinoid, gastrointestinal stromal tumor (GIST) sarcoma, and melanoma. The symptoms caused by these lesions are often initially attributed to a range of benign conditions such as hemorrhoids, so that it is not uncommon that these unusual cancers are often diagnosed in more advanced stages. This chapter reviews the presenting symptoms, diagnosis and treatment specifically of rectal carcinoid, GIST, sarcoma and melanoma and provides a brief literature review concerning the most up-to-date management regimens for each of these tumour types.

Carcinoid Tumors

Carcinoid tumors, (also called neuroendocrine tumors or NETs), are tumors with malignant potential arising from enterochromaffin (Kulchitsky) cells in the crypts of Lieberkuhn found in epithelial organs throughout the body [2]. These cells represent part of the amine precursor uptake and decarboxylation (APUD) system which are responsible for the synthesis of a wide variety of biogenic amines, peptides and neurotransmitter substances. These tumors were first described in 1867 and defined histopathologically in 1888 but the term “carcinoid” or “carcinoma-like” was not coined until 1907 by Oberndorfer [3, 4]. The location of carcinoid tumors is an important factor in determining prognosis and survival [5]. After the appendix

E. B. Sneider · J. A. Maykel (✉)
Department of Surgery, Division of Colon and Rectal Surgery, University of Massachusetts Medical School, Worcester, MA, USA
e-mail: maykelj@ummhc.org

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(35%) and the small bowel, (23%) the rectum is the third most common location for gastrointestinal carcinoids representing 21% of cases [2, 6]. While rectal carcinoids comprise only 1–2% of all rectal tumors and 12.6% of all carcinoid tumors, the incidence has been increasing [5, 7, 8]. In a retrospective study of 4613 patients with rectal carcinoids, Taghavi et al. demonstrated an increased detection rate of carcinoid tumors following the widespread use of screening colonoscopy after the year 2000 [5, 9].

The 5-year survival rate for all rectal carcinoid tumors has been reported to be as high as 88%, which is higher than the 5-year survival rate for carcinoids in other locations (67%). The higher 5-year survival rate for rectal carcinoids is thought to be related to the small size of most rectal carcinoids which are therefore typically more localized at the time of presentation [3, 10]. More advanced carcinoid tumors in the rectum can invade through the muscularis mucosa into the submucosa and can present with metastasis in between 4% and 18% of patients [11]. There is no specific sex predominance and the average age at diagnosis is lower than that seen with colonic carcinoids (48–52 years). Moreover, the incidence rates are three to fourfold higher in African Americans when compared to other ethnicities [11].

The terminology pertaining to carcinoid tumors has changed significantly over the years. The first World Health Organization (WHO) classification of endocrine tumors in 1980 applied the term carcinoid to most NETs and divided them into one of three categories; namely, enterochromaffin (EC) cells, gastrin (G) cells or unspecified. This terminology led to confusion amongst pathologists and clinicians, resulting in a change in nomenclature at the time of the WHO update in 2010 [12]. The revised WHO classification uses the terms “neuroendocrine tumor” and “neuroendocrine carcinoma”. A distinction is made between well-differentiated NE tumors (benign behavior or uncertain malignant potential), well-differentiated NE carcinomas (low-grade malignancy) and poorly differentiated NE carcinomas (high-grade malignancy) [11].

Symptoms

Most patients with rectal carcinoids are asymptomatic, with lesions detected during routine digital rectal examination (DRE) or by screening examination with colonoscopy or sigmoidoscopy [11]. If symptoms are evident at the time of presentation, they may include anorectal discomfort, constipation, bleeding and/or change in bowel habit. Such symptoms are usually due to local tumor mass effects, the result tumor fibrosis, or the systemic impact of secreted bioactive products such as serotonin, histamine, tachykinins, and prostaglandins with such bioactive products secreted from carcinoid tumors in approximately 10% of patients. The symptoms of carcinoid syndrome although well described can be protean and include flushing and diarrhea, although this latter symptom is extremely rare in the setting of a hindgut carcinoid without associated extensive hepatic metastases.

Reports have shown that the incidence of lymph node metastasis for rectal carcinoids smaller than 10 mm is less than 3%, but that the incidence of lymph node metastasis increases as the tumor size increases where it may be as high as 80% in those tumors greater than 20 mm in maximal diameter [10, 13]. Both a tumor size exceeding 10 mm and lymphatic invasion have been reported as independent predictors of lymph node metastasis, whereas a tumor size greater than 20 mm and venous invasion are both predictive of distant metastasis [13]. Other risk factors for metastases include an atypical tumor surface, patient age greater than 60 years and muscle, perineural and/or lymphovascular invasion. The factors that have been shown to be associated with worse survival include large tumor size, muscle layer invasion and the presence of metastases [3].

Diagnosis

On colonoscopy, these submucosal lesions are typically small, mobile, round, well-circumscribed lesions that are typically yellowish in color due to their high lipid content [2, 11, 14]. Often, these lesions are <2 cm in size [2]. Further evaluation of patients with carcinoid tumors relies on biochemical studies and topographic localization of the primary lesion and potential metastatic disease. Several biologic markers can be used to aid in the diagnosis and determination of activity of rectal carcinoid tumors. Urinary 5-HIAA is a marker that can be measured in a 24-h urine collection and has a specificity of approximately 88%. As hindgut/rectal carcinoids lack the enzyme DOPA decarboxylase and cannot convert 5-hydroxytryptophan (5-HT) to serotonin, they only rarely secrete serotonin and therefore 5-HIAA levels tend to be normal [11]. Additionally, there are many drugs and serotonin-rich foods that can falsely elevate the level of 5-HIAA in the 24-h urine collection making this test only occasionally useful with limited specificity. Chromogranin A (CgA) is a water-soluble glycoprotein stored in the secretory granules of NE cells and released by NETs, making it a reliable tumor marker used for detection and monitoring of carcinoids. As CgA concentration has been shown to correlate with tumor burden, it is a useful tool to follow the patient for recurrence following resection [11].

A variety of radiographic imaging including CT scan, MRI, PET CT, and octreotide scanning can be employed in the evaluation of the primary lesion and in the exclusion of metastatic disease. Classic findings of carcinoid on CT scan and MRI include the presence of a mass lesion that is associated with calcification and radiating strands of fibrosis and spiculation. The degree of radiating strands detected by CT scan has been found to correlate with the degree of fibrosis seen at the time of operative intervention. Mesenteric lymph node metastases are accurately detected by CT scan 91% of the time when present. Studies comparing the diagnostic efficacy between CT scan and MRI have not shown that one test is better than the other in terms of diagnosing carcinoid tumors [11]. Somatostatin receptor scintigraphy (or ^{111}Indium-octreotide scanning) is an imaging study which uses ^{111}In-labeled somatostatin analogue in order to detect somatostatin receptor-positive tumors, such

as carcinoids. One advantage of this test is that it scans the entire body; therefore both the primary lesion and metastatic disease may be identified [15]. Because the overall sensitivity is high, (ranging between 80 and 90%), it is felt that the octreotide scan should be used as the initial imaging method in patients with carcinoids [11, 16]. While both CT and MRI are used for the detection and initial localization of carcinoid tumors or metastases, their detection rates and sensitivities are lower than the hormone-based imaging methods where the median detection rates and sensitivity of CT and/or MRI are both 80% in contrast to an 89% detection rate and an 84% sensitivity with ^{111}Indium-octreotide scanning. PET CT scanning is not recommended in the routine evaluation of rectal carcinoids as NETs are usually well-differentiated tumors that are typically slow growing with a low metabolic rate, so that FDG uptake is not strong enough and where detection rates range from only 25 to 73% overall [11]. Endorectal ultrasound (ERUS) is of course useful in the assessment of rectal lesions in order to determine submucosal infiltration with breaching of the hyperechoic submucosal layer, assisting in the decision in selected cases for definitive treatment by endoscopic polypectomy or transanal endoscopic microsurgical excision [10, 17].

Treatment

Several treatment options exist for carcinoid tumors, ranging from surgical resection to somatostatin receptor-targeted therapy. Surgery is the most effective treatment for both local tumor symptoms (such as obstruction and bleeding) as well as symptoms caused by the tumor secretory agents.

Based upon the understanding of an increased likelihood of lymph node metastasis with larger rectal carcinoids, treatment guidelines vary based upon the size of the primary tumor. Rectal carcinoids less than 10 mm with no obvious lymphatic involvement are definitively treated with transanal local excision, either endoscopically or surgically. Tumors greater than 20 mm should be treated with a formal oncologic resection, such as low anterior resection (LAR) with total mesorectal excision (TME) or by abdominal-perineal resection (APR) with TME. Treatment of rectal carcinoids between 10 and 20 mm in size remains controversial. In this group, options include a conservative approach with local surgical resection or a more aggressive approach with a formal TME. In this respect, [10] and the New Orleans Louisiana Tumor Specialist (NOLANETS) Group conducted a review based upon their clinical experience at a large tertiary care center in order to determine the clinical impact of tumor size on nodal positivity with the goal of determining whether intermediate-sized rectal carcinoids should be treated with formal TME rather than local excision. Of the 62 patients included in the study, 13 had tumors in the intermediate category with sizes ranging from 1.1 to 2 cm. In this group, 69% had lymph node metastasis, which suggests that the intermediate sized lesions may behave more aggressively than previously reported and therefore would demand a more radical initial surgical intervention with formal TME.

Gleeson et al. [14] from the Mayo Clinic also reviewed their 12-year experience with NETs of the rectum in order to determine if intermediate-sized (11–19 mm) tumors had a natural history similar to tumors ≥20 mm. They found that intermediate well-differentiated carcinoid tumors mimicked the behavior of larger (>20 mm) lesions with respect to metastasis rate and disease progression and as a consequence, recommended a more aggressive approach to initial staging and management of these lesions. For lesions ranging from 11 to 19 mm that are limited to the mucosa/submucosa (T1), they recommended endoscopic or transanal excision followed by a close surveillance protocol with annual clinical and radiographic assessment. For lesions ranging from 11 to 19 mm that are T2 or greater or if lymph node involvement is present, they recommended either LAR or APR with TME.

Hepatic metastases from carcinoid can be treated by surgical resection or by radio-frequency ablation, cryoprobe ablation, hepatic artery occlusion therapy, or transplantation when disease is more advanced or widespread [6, 11]. The goal of these therapies is to debulk the tumor mass in order to reduce symptoms, facilitate pharmacologic management and prolong survival. The responses to chemotherapeutic agents, such as streptozotocin, 5-FU, doxorubicin, and cyclophosphamide are somewhat heterogeneous and are influenced by tumor differentiation and grade as well as by tumor site with poorly differentiated variants sometimes showing limited responses to platinum-based regimens [10]. The use of Streptozotocin is restricted because of its toxicity, most notably myelosuppression and renal failure. Although chemotherapeutic responses are generally low it may be useful in selected symptomatic cases with disease progression, poor differentiation and clinical aggression. By contrast, the principal agents used in this setting are Somatostatin analogs which include octreotide and lanreotide, both of which can be used in the treatment of carcinoid syndrome [2, 11, 18]. The CLARINET study is a randomized, double-blind, placebo-controlled trial of lanreotide in advanced (moderately and well-differentiated) cases with non-functioning NET tumors with low proliferative indices where there initially appears to be advantage for lanreotide over placebo in progression-free survival without an impact on HRQOL [19]. The role of VEGF-receptor targeted therapy (Bevacizumab) and tyrosine kinase inhibition (Sunitinib, Pazopanib) given the high vascularity of NETs is at present unclear with the results of ongoing trials awaited.

Gastrointestinal Stromal Tumors (GISTs)

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the GI tract. Whilst they are most often seen in the stomach (60%) and the small intestine (30%), GISTs of the colon and rectum comprise 5% of tumors overall with those in the rectum exceeding the number of colonic GISTs [20, 21]. GIST tumors arise from the interstitial cells of Cajal located in the myenteric plexus of the gut wall [22]. These cells express cell surface markers, such as CD34 and CD117 (c-KIT), which are important in the diagnosis and treatment of all

GISTs [20, 22]. Rectal GISTs generally display a male predominance with occurrence most commonly in adults between the ages of 17–90 (mean age of 59 years). Most cases are sporadic although there are families with a germline KIT or PDGFRA mutation as well as an association of GISTs with von Recklinghausen's disease and Carney's triad (gastric GIST, paraganglionoma and pulmonary chordoma) [23].

Symptoms and Diagnosis

Small rectal GISTs are often asymptomatic whereas larger masses can be the cause of pain and rectal bleeding, even resulting in obstruction. The imaging modalities most commonly used in the evaluation of GISTs include CT, MRI, and endorectal ultrasound (ERUS). On CT and MRI, GIST tumors appear as a solid, hyperdense enhancing mass without surrounding lymphadenopathy (Fig. 30.1). ERUS confirms that the tumor originates from the muscularis propria. Biopsy of these lesions before treatment remains controversial because they are soft, friable tumors and biopsy may cause bleeding or tumor rupture ultimately leading to seeding of the tumor along the biopsy tract [23–25].

In this setting, the two most important prognostic factors for GIST tumors are tumor size and mitotic index (number of mitoses per 50 high power field – HPF). By definition, low-grade tumors have a mitotic rate ≤5 per HPF whereas high-grade tumors have a mitotic rate >5 per HPF. The most specific marker for GISTs is the tyrosine kinase proto-oncogene CD117 (c-KIT), which is present in approximately 95% of all cases with CD34 (haematopoietic progenitor cell antigen – cluster differentiation glycoprotein) reported as detected in close to 100% of rectal GISTs.

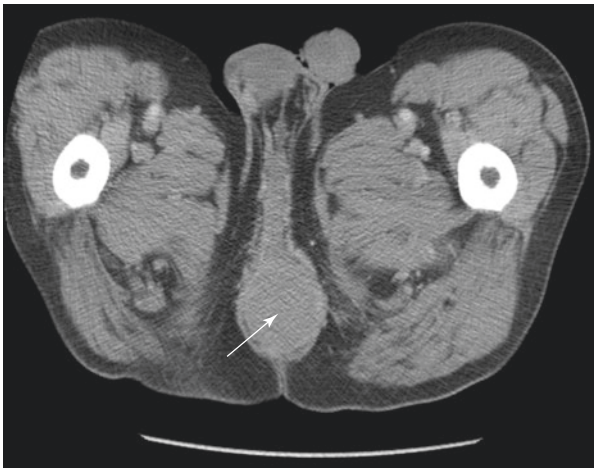

Fig. 30.1 CT scan imaging of a rectal GIST (arrow)

Treatment

Some aspects of the management remain controversial although there are agreed principles with surgery being the mainstay of therapy. The goal of surgery is complete *en bloc* resection of all gross disease including involved adjacent structures [26, 27]. Options for resection of rectal GISTs include transanal excision, transanal endoscopic microsurgery (TEM), low anterior resection (LAR) and abdominal perineal resection (APR) [2]. As GISTs do not spread via lymphatics, lymphadenectomy is unnecessary.

When deciding on the appropriate operative approach, one must consider whether or not the tumor is low, intermediate or high-risk based upon the size of the tumor and its mitotic index. Transanal excision of rectal GISTs is recommended for tumors that are not high-risk and which are located within 5 cm of the anal verge (Fig. 30.2) [28]. Either LAR or APR should be reserved for locally advanced lesions, recurrent tumors of the low rectum, or large tumors of the low rectum that are resistant to tyrosine kinase inhibitor treatment [20, 28]. Regular follow-up at 3–6 month intervals in the first three postoperative years should be performed for these patients [29].

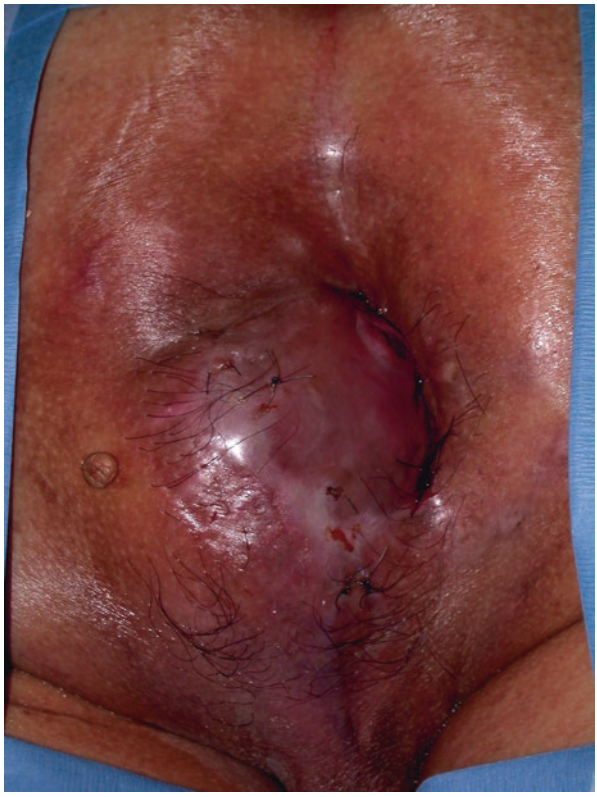

Fig. 30.2 Perianal GIST. (Courtesy of Scott Steele, MD Cleveland Clinic Ohio)

Imatinib (Gleevec) is a tyrosine kinase inhibitor that targets c-KIT-positive GIST tumors and has an important and evolving role in the management of these patients. Neoadjuvant treatment with imatinib is useful for larger GISTs in order to downsize the tumor and improve the possibility of a complete resection with negative (R0) margins [2, 20, 22, 28, 30]. According to the results of the ACOSOG Z9001 study, the indications for adjuvant treatment with imatinib for at least 1 year include those patients with intermediate or high-risk for recurrence GIST tumors, incomplete surgical resection or in circumstances when tumor rupture has occurred during excision [31]. This multi-institutional USA trial also demonstrated that use of adjuvant imatinib improves disease-free but not overall survival.

Liu et al. performed a retrospective review of 21 cases of rectal GIST at a single institution in Hunan Province in order to explore optimal treatment strategies. Preoperative treatment with imatinib was given if the tumor size was greater than 5 cm and located in the lower rectum, if the tumor size exceeded 5 cm in the pelvis, or if the tumor size was larger than 5 cm and located adjacent to the prostate. Five patients received preoperative imatinib treatment of 400 mg/day for 6–8 months in order to downsize the tumor and all patients showed a partial response. Amongst the patients with tumors >5 cm, those who received preoperative imatinib therapy had a significantly higher rate of negative resection margins than those without preoperative imatinib therapy ($P = 0.04$). The indications for adjuvant imatinib therapy included all patients in the intermediate or high-risk groups for tumor recurrence and those patients with either an R1 or R2 resection of the tumor. Patients in the intermediate or high-risk group who received adjuvant imatinib therapy had a significantly longer disease-free survival than those patients who did not receive imatinib therapy [28]. These findings are in accordance with other sporadic reports of the selective advantage of neoadjuvant therapy for tumors with predictably worse prognosis [32, 33].

Sarcoma

Sarcomas are malignant tumors arising from mesenchymal tissue and represent 0.5% of all rectal neoplasms [33]. These tumors are classified into different histological types, including leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, Ewing sarcoma, Kaposi's sarcoma (notably in HIV-positive patients) and malignant fibrous histiocytoma [34, 35].

Symptoms and Diagnosis

The most common symptom at the time of presentation is rectal bleeding due to the presence of mucosal ulcerations. Other symptoms include anorectal pain, tenesmus, urgency, fecal incontinence and change in bowel habits. Diagnostic tools used for

rectal sarcoma are similar to those used to diagnose other rectal tumors and include digital rectal examination, sigmoidoscopy, colonoscopy, ultrasound, CT, MRI, and PET CT (Fig. 30.3). Colonoscopy may reveal a polypoid or submucosal lesion that is often associated with mucosal ulcerations. Endorectal ultrasound typically reveals a hypoechoic, heterogenous mass within the muscularis propria [36, 37]. Grade I tumors are well differentiated, grade II tumors are moderately differentiated and grade III tumors are poorly differentiated. The size, depth of invasion, and histologic grade are the most important prognostic factors [35, 38].

Treatment

The mainstay of treatment for rectal sarcoma is surgery, with wide *en bloc* resection resulting in negative margins. Most recently this has been reported with the transanal total mesorectal excision technique [39]. Specific recommendations regarding

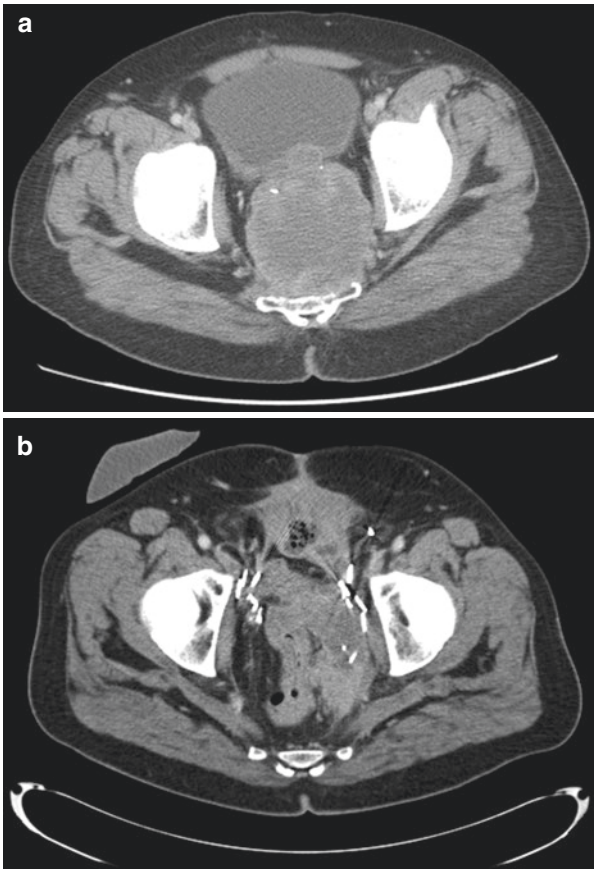

Fig. 30.3 (**a**, **b**) CT scan imaging of rectal sarcoma

the extent of resection continues to remain controversial and depends upon the size of the lesion, the mitotic rate and the tumor location. Certain types of rectal sarcoma, especially those involving the sphincter complex, can be treated with neoadjuvant chemotherapy and radiotherapy [38] with chemotherapeutic options including vincristine, cyclophosphamide, actinomycin D and doxorubicin.

Melanoma

Melanomas of the gastrointestinal tract can be divided into those either metastatic from cutaneous neoplasms or more rarely a primary gastrointestinal melanoma. Rectal melanoma is an extremely rare and aggressive malignancy comprising 0.05% of all malignant colorectal neoplasms [40]. The anorectum is the third most common mucosal site for melanoma, following the head and neck and the female genital tract. When compared with cutaneous melanomas, melanomas of the GI tract carry a far worse prognosis which has been thought to be associated principally with a delay in their diagnosis. The first case of anorectal malignant melanoma was reported by Moore in 1857 [41]. While isolated cases have been reported in the literature in the pediatric population, rectal melanoma is more commonly seen in elderly patients between the 6th and 8th decades of life [42]. Because of the aggressive nature of the tumor, 67% of patients are found to have distant metastatic disease at the time of initial presentation with a median overall survival between 8 and 18 months [41]. The 5-year overall survival is estimated to be only 6% [2] whilst patients without lymph node metastasis have a 5-year survival of 20% (compared with 0% in patients with metastases) [43].

All melanomas originate from melanocytes. In the rectum, melanocytes are found at the anal transition zone. These melanomas drain submucosally to the inguinal and inferior mesenteric lymph nodes and subsequently to the hypogastric and paraaortic lymph node basins [44]. When compared with melanomas induced by sun damage, mucosal melanomas exhibit a different pattern of genetic abnormality and are not predisposed in patients of fair skin. Moreover, some evidence has suggested that infection with the human immunodeficiency virus (HIV) may increase a patient's risk for the development of anorectal melanoma suggesting a secondary role for immunosuppression [45].

Symptoms and Diagnosis

Usually symptoms related to rectal melanoma are non-specific and similar to hemorrhoidal symptoms, prolonging the time until these patients seek medical attention [46]. While the most common presenting symptom is bleeding, other symptoms include tenesmus, pruritus, change in bowel habits and pain. Diagnosis can be difficult with melanoma of the rectum because 87% of these lesions are amelanotic, therefore

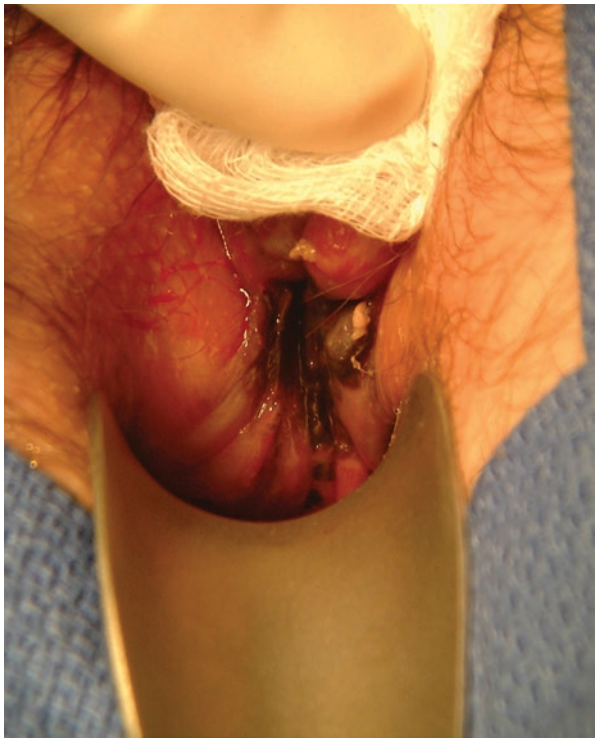

Fig. 30.4 Melanotic anal melanoma. (Courtesy of Scott Steele, MD Cleveland Clinic Ohio)

they are often missed on visual inspection [45] (Fig. 30.4). Methods used for diagnosis include DRE, anoscopy, proctoscopy, flexible sigmoidoscopy, colonoscopy and ERUS. Staging evaluation utilizes CT, MRI or PET-CT scans in order to determine if there is lymphadenopathy or metastasis to the liver, lung or pelvis. Tumor thickness and lymph node involvement in cutaneous melanoma is extremely important in terms of staging and prognosis, but in rectal melanoma, reporting of tumor thickness within the literature has been inconsistent [41, 43, 45]. Histologic markers, such as melanin, S-100, HMB-45 and vimentin, can also be used to aid in the diagnosis of rectal melanoma [43]. Most patients with distant metastatic disease have hepatic metastases followed in incidence by pulmonary and bone metastases [40].

There are two different staging systems for rectal melanoma. The first is the American Joint Commission on Cancer (AJCC) staging which is based on the presence of tumor in lymph nodes and the depth of the primary tumor whereby: Stage IA is localized disease measuring 0.75 mm deep, Stage IB is localized disease 0.76–1.5 mm deep, Stage IIA is localized disease 1.5–4 mm deep, Stage IIB is localized disease >4 mm deep, Stage III regional node involvement and Stage IV distant metastatic disease [46]. Another staging system has been suggested by Caravajal et al. [47] which is a 3-level staging system where Stage I represents local disease with tumor growth limited to the bowel wall, Stage II has regional lymph node metastases and stage III disseminated disease extending past the surgical resection margin [40, 43, 46, 47].

In 2013 Falch et al. [40] performed an extensive 45-year review of anorectal malignant melanoma and proposed a third staging classification for this disease. Their rationale was that a TNM classification does not exist and despite the more recent AJCC staging system, most cases of rectal melanomas are classified based on the dated 40-year-old 3-level staging system which does not utilize histopathologic parameters to help guide treatment decisions. It has been shown that patients have a poorer survival rate with increasing depth of invasion of the tumor into the bowel wall resulting in their proposed staging system is as follows: Stage 1- local tumor spread without infiltration of the muscular layer; Stage 2 – local tumor spread with infiltration of the muscular layer; Stage 3 – regional tumor spread and/or positive lymph node metastases and Stage 4 – disseminated tumor spread.

Treatment

Treatment options for rectal malignant melanoma include surgical resection, chemotherapy, radiotherapy and immunotherapy either alone or in combination [48]. There is debate in the literature regarding the extent of resection required for optimal treatment of rectal melanoma [44], and as to whether a radical resection with APR is needed or whether WLE is adequate surgical treatment for this highly aggressive disease. Because of the rarity of this disease, treatment guidelines are based upon small retrospective studies with no prospective randomized controlled clinical trials comparing overall survival between APR and WLE. In this context, APR has traditionally been considered the standard treatment for rectal melanoma but data does not support an overall survival advantage over a less aggressive approach with WLE [40, 44]. Accordingly, the less radical resection with WLE is gaining popularity due to the benefits of quicker recovery, minimal impact on bowel function and avoidance of a colostomy [41, 43, 49, 50]. General resection margin guidelines for rectal melanoma are: 1 mm tumor = 1 cm margin; 1–4 mm tumor = 2 cm margin; >4 mm tumor = an APR is recommended [43]. The recurrence rate after WLE is approximately 60%, which is comparable to that following an APR [50] although it is suggested that APR provides better local control.

Utilizing the proposed staging system by Falch et al., an algorithm has been developed for the diagnosis and treatment of rectal malignant melanoma. For stage 1 tumors, they recommend an APR because as their literature review showed significantly better survival compared with those with more advanced disease. Patients with stage 2 disease are recommended to undergo WLE plus adjuvant radiotherapy or APR in the palliative setting. Patients with stage 3 disease should undergo WLE plus adjuvant radiotherapy and those with stage 4 disease should undergo WLE with or without adjuvant radiotherapy or palliative APR for symptom management. Sentinel lymph node (SLN) biopsy and lymph node dissections are well described in the literature for cutaneous melanoma but their role in the management of rectal melanoma has yet to be determined [41, 51]. It is known that mesorectal, pelvic sidewall, and inguinal lymph nodes are at increased risk for metastases from rectal lesions. In an APR, the mesorectal lymph nodes are resected *en bloc* as part of

the TME. Prophylactic bilateral inguinal lymphadenectomy in patients with clinically non-palpable nodes has not been shown to improve survival, and carries high morbidity with problematic wound healing and lymphedema [44]. Although inguinal metastases represent locoregional disease in squamous carcinoma of the anus, their presence in anorectal melanoma is more indicative of systemic disease spread. Locoregional lymphadenectomy has no effect on outcome as it does for cutaneous melanoma with occult nodal metastases, however, in patients with clinically palpable disease, elective lymph node dissection should be considered [52].

With such poor results following surgery alone, additional therapies have been evaluated, including chemotherapy and radiotherapy. Radiation can be given as either neoadjuvant or adjuvant treatment following APR or WLE but so far its use in different settings has not been shown to provide any significant clinical benefit [43]. The dosing and fractionation of radiation for rectal melanoma is 30 Gy in 5 fractions. Chemotherapeutic agents used as adjuvant therapy in the treatment of rectal melanoma include cisplatin, vinblastine, dacarbazine, interferon B and IL-2. Dacarbazine is the most widely used single agent in the treatment of rectal melanoma and it has been associated with a response rate of approximately 20%. Unfortunately, the response duration is only 4–6 months and there have not been any prospective, randomized controlled trials supporting a survival benefit for dacarbazine over placebo [44].

Conclusion

Adenocarcinoma is the most commonly diagnosed neoplasm of the rectum. It is important to remember, however, that other malignancies can develop in the rectum, such as carcinoid, GIST, sarcoma and melanoma. The rectum is also the seat of both primary and secondary lymphoma usually of non-Hodgkins B cell type [53] as well as those lymphoma cases associated with inflammatory bowel disease and HIV-AIDS. AIDS-related Kaposi's sarcoma (either isolated or with disseminated GI involvement) has been described and often precedes cutaneous involvement [54, 55]. Many of the presenting symptoms of these unusual rectal tumors overlap with the more common benign anorectal diseases such as hemorrhoids so that complete clinical evaluation should not be delayed particularly in conditions such as inflammatory bowel disease where symptoms may be attributed to underlying proctitis and where the possibility of a 'collision' lesion may not have been considered.

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Part X
Survivorship and Quality of Life Considerations

Chapter 31
Rectal Cancer Survivorship and Quality of Life

Zaid Abdelsattar and Scott Regenbogen

Introduction

Colorectal cancer is the third most common cancer and the second leading cause of cancer-related death in the United States. With advances in early cancer detection, multi-modality therapy and surgical techniques, the overall 5-year survival for colorectal cancer across all stages now averages 65% [1]. As a result, there are more than 1.2 million colon or rectal cancer survivors currently living in the United States [2, 3] and with this rapidly growing population of survivors, there is an increasing awareness that a more comprehensive cancer care management protocol needs to expand in order to account for the needs of colorectal cancer survivors and to equate the impact of treatment on quality of life outcomes.

Cancer survivorship, in this context, must therefore include not only surveillance and the treatment of recurrence, but must also pay attention to parameters of quality of life as specifically affected by surgery and adjuvant therapies. This kind of analysis needs to consider amelioration of long-term treatment-related toxicity and cancer-related disability, eventually transitioning back to preventive health screening measures and the effectiveness of primary care initiatives. Survivorship after therapy for rectal cancer brings unique challenges, in particular because of the relatively long duration of surgical and adjuvant therapy in some cases, the added concerns regarding both locoregional and systemic recurrence, the impact of defecatory and sexual dysfunction and, for some, the necessity of living with a stoma [4]. Although some rectal cancer survivors recoup with a renewed sense of life, more often than not, their cancer and its treatment have taken a significant toll on their health, functioning, sense of security, personal independence and overall well-being.

Z. Abdelsattar
Mayo Clinic, Rochester, MN, USA

S. Regenbogen (✉)
University of Michigan, Ann Arbor, MI, USA
e-mail: sregenbo@med.umich.edu

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Sequelae which affect long-term function and outcome may become apparent shortly after the cessation of therapy or may arise some years later. The issue of such assessment is complex where even personal relationships can change requiring adaptations to new routines and novel work opportunities and modifications. As a consequence, the interpretation of data may be difficult and accordingly, monitoring for late and long-term treatment-related effects, regular repeated determinations of validated quality of life (QOL) parameters, assessments of the maintenance of general health and the management of the social and psychological aspects of cancer recovery, rehabilitation, adjustment and re-integration into normal daily life have become vital concerns which can be addressed by cancer survivorship care [5, 6].

This chapter addresses the unique aspects and challenges of rectal cancer survivorship and the issues pertaining to post-treatment surveillance. The issues frequently affecting the QOL following treatment and the late and long-term effects of such treatments are outlined along with recommended lifestyle interventions and models of care for rectal cancer survivors.

Challenges in Rectal Cancer Survivorship

Because rectal cancer therapy requires the expertise of a variety of specialists often practicing in different settings, it exemplifies the potential "quality chasm" that exists in the U.S. health care system and the need for health insurance reforms and innovations in health care delivery [7]. Without careful coordination, rectal cancer survivors can be lost to systematic follow-up and opportunities to effectively intervene may be readily missed. Many patients complete cancer treatment unaware of their heightened health risks and ill-prepared to manage their future health care needs. Furthermore, recommended follow-up care is often not delivered and the psychosocial needs of cancer patients are often not addressed.

Several organizations, such as the National Cancer Institute and the American Cancer Society have invested in broad cancer survivorship initiatives and care plans. Similarly, multiple survivorship advocacy groups, such as the National Coalition of Cancer Survivorship [8] and the Livestrong Foundation [9], have arisen in order to address some challenges pertaining to cancer survivors. However, widespread implementation of structured survivorship programs has yet to gain momentum and the role of survivorship care in the typical approach to rectal cancer patients currently remains undefined.

In an attempt to raise awareness and bring cancer survivorship to a higher priority nationally, the Institute of Medicine (IOM) established a set of recommendations in its report *From Cancer Patient to Cancer Survivor: Lost in Transition* (Table 31.1) [10]. While some of these recommendations are easily achievable, several others require restructuring of the care delivered by cancer providers as well as significant commitments from government funding sources and other stakeholders traditionally invested in cancer care. Similarly, the American College of Surgeons Commission

Table 31.1 Institute of Medicine recommendations for cancer survivorship: summary

Recommendation 1	Raise awareness of the needs of cancer survivors, establish cancer survivorship as a distinct phase of cancer care and act to ensure the delivery of appropriate survivorship care
Recommendation 2	Provide a comprehensive care summary and follow-up plan (survivorship plan) that is clearly and effectively explained to all patients completing active cancer therapy
Recommendation 3	Use systematically developed evidence-based clinical practice guidelines, assessment tools and screening instruments to help identify and manage late effects of cancer and its treatment
Recommendation 4	Develop quality of survivorship care measures and implement quality assurance programs to monitor and improve the care that all cancer survivors receive
Recommendation 5	Test models of coordinated, interdisciplinary survivorship care in diverse communities and across systems of care
Recommendation 6	Develop comprehensive cancer control plans that include consideration of survivorship care, and promote the implementation, evaluation and refinement of existing state cancer control plans
Recommendation 7	Expand and coordinate efforts to provide educational opportunities to health care providers to equip them to address the health care and quality of life issues facing cancer survivors
Recommendation 8	Act to eliminate discrimination and minimize adverse effects of cancer on employment, while supporting cancer survivors with short-term and long-term limitations in ability to work
Recommendation 9	Act to ensure that all cancer survivors have access to adequate and affordable health insurance with the assistance of insurers and health care payers
Recommendation 10	Increase funding support of survivorship research and expand mechanisms for its conduct to better guide effective survivorship care

on Cancer (CoC) has recently published three new Program Standards for the continuum of care for cancer patients (Practice Standard 3.1: Patient Navigation; 3.2: Screening for Psychosocial Distress and 3.3: Providing Treatment Summaries and Survivorship Care Plans) [11]. Implementing these Program Standards have become necessary for CoC accreditation as of 2015.

In this respect, only 37% of currently CoC-accredited cancer centers believe that they would be able to comply with Program Standard 3.3, which requires a Cancer Committee within any institution to specifically develop and implement a formal process for disseminating a comprehensive care summary along with provision of a regimented follow-up plan for cancer patients completing treatment. A myriad of barriers to the implementation of this sort of program have become evident with the added problems of time constraints in coordination and secondary financial and human resource limitations on program enactment and during monitoring [12]. Notwithstanding these challenges, survivorship care models are being widely promoted with the intent of highlighting the importance of survivorship care and improving its efficiency, effectiveness and reach [13–17].

Cancer Surveillance

Following curative-intent therapy for rectal cancer, the goal of surveillance is to identify treatable local or systemic recurrence as well as metachronous colorectal malignancy. In general, the surveillance approach includes all of the measures used in the surveillance of colon cancer, plus additional endoscopic and/or imaging measures designed to evaluate specifically for local pelvic recurrence, especially following sphincter-sparing, restorative resections. This issue is in part covered in Chap. 3 on Imaging as well as in other sections of this book.

The use of follow-up studies after curative resection of rectal cancer is highly variable across providers and overall compliance with surveillance guidelines is low. In general, only about one quarter of patients will receive recommended surveillance for colorectal cancer and compliance is less than 10% amongst those patients who are not under the care of an oncologist [18]. Multiple surveillance strategies have been suggested at costs ranging from a few hundred to several thousand dollars per patient and in this climate the optimal surveillance strategy remains highly controversial with various international specialty societies, institutions, and countries reporting competing recommendations [19]. In this chapter, we summarize the pertinent evidence concerning surveillance strategy, generally following the recommendations of the National Comprehensive Cancer Network (NCCN) which advocates a high-intensity surveillance policy (Table 31.2) [20].

Several studies designed to compare low-intensity with high-intensity surveillance strategies have demonstrated the clear advantages of an intensive strategy for the detection of asymptomatic recurrences at an earlier stage, effectively offering patients the best chance for cure. Moreover, this more intensive approach has shown in examination a modest but significant survival advantage [21–23]. This effect is especially apparent in the first 3 years following resection of the primary; a time

Table 31.2 National Comprehensive Cancer Network (NCCN) post-treatment surveillance recommendations

Modality	NCCN recommendation
History and physical examination	Every 3–6 months for 2 years, then every 6 months for 3 years
CEA testing	Every 3–6 months for 2 years for ≥T2 disease; then every 6 months for 3 years
CT scanning	Abdomen/pelvis and chest annually for up to 5 years; For resected metastatic disease, abdomen/pelvis and chest every 3–6 months for 2 years, then every 6 months up to a total of 5 years
Endoscopic surveillance	Colonoscopy at 1 year; Subsequent studies dictated by prior findings If no advanced adenoma, repeat at 3 years, then every 5 years; if advanced adenoma at one year with a repeat at one year. Proctoscopy every 6 months for 3–5 years for rectal cancer if status is post-low anterior resection or trans-anal excision

when 80% of recurrences typically occur [24]. A meta-analysis of five major randomized trials by Renehan et al. [25] comparing low-intensity and high-intensity surveillance strategies, demonstrated a significant reduction in all-cause mortality, with earlier detection of all cancer recurrences and an increased detection rate for local cancer recurrences. In this respect, the improvement in overall survival rates have been most pronounced in those studies which incorporate frequent carcinoembryonic antigen (CEA) measurements with computed tomography (CT) as part of their more intensive follow-up schedules. Concerning this point, in a single-institution study reported from Buffalo New York by Fora et al. [26] among patients undergoing intensive surveillance, more than half of the recurrences were detected when they were potentially amenable to repeat resection with curative intent.

By contrast, however, a recent trial by Primrose and colleagues [27] has demonstrated that amongst patients who had undergone curative surgery for primary colorectal cancer that there was no survival advantage in combining both CEA and CT imaging in the intensive strategy. These results would suggest that monitoring with CEA combined with a single CT scan at 12–18 months is not any more advantageous over regular CT scanning and in this context, since CEA testing can be performed simply in the primary care setting, this approach might potentially be more cost-effective. As it stands today, there is considerable controversy regarding the selection of the optimal strategy for following patients after potentially curative rectal cancer surgery where the NCCN panel recommendations as mentioned in this chapter only reflect an expert consensus rather than the result of a prospective randomized trial approach.

Surveillance colonoscopies aim to detect and remove metachronous polyps since patients with a history of colorectal cancer have an increased risk of developing second cancers. A full colonoscopy is recommended at approximately 1 year following resection (or at approximately 3–6 months following resection if not fully performed preoperatively due to an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy detects and excises an advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia), in which case, colonoscopy should be repeated in 1 year [28]. More frequent colonoscopies may be indicated in patients who present with colorectal cancer before age 50 [28]. Proctoscopy is recommended every 6 months for 3–5 years in order to evaluate for local recurrence at the rectal anastomosis for patients who have undergone a sphincter preserving operation [29].

The utility of endorectal ultrasound (ERUS) in routine surveillance following curative rectal cancer surgery is not clear [15], although there are some retrospective studies which suggest its overall usefulness [30]. ERUS can evaluate cases for extra-mural and sub-mucosal recurrences, which may otherwise be missed on regular endoscopy and which can permit ultrasound-guided biopsy [31, 32]. When combined with fine-needle aspiration and biopsies, this technique can differentiate an early recurrence from postoperative changes and post-radiotherapeutic effects both of which can be indistinguishable on routine imaging. Prospective trials are needed, however, to establish the role of ERUS in routine surveillance as there is currently no formal recommendation to guide its use.

Chest, abdomen, and pelvis CT scans are recommended annually for 5 years in stage II and stage III patients. CT imaging is recommended so as to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver. Consequently, CT scan is not routinely recommended in patients who are not candidates for potentially curative resection of such liver and/or lung metastases. Pelvis CT scans are used for the assessment of locoregional recurrence. The routine use of PET/CT to monitor for disease recurrence is not recommended at present in the absence of the clinical suspicion of an occult recurrence. Similarly, pelvic MRI has little to offer as a routine surveillance tool following curative surgery for rectal cancer unless there are specific symptoms. In this respect, its cost, the presence of high false positive rates, and the resultant patient anxiety would appear to offset any minimal benefit its use may add [33]. Pelvic MRI is therefore reserved for additional imaging to aid in operative extirpative planning (multivisceral and exenterative) for cases with CT-detected pelvic recurrences [34, 35].

The management of patients with an elevated CEA level following resection should include a thorough history and physical examination; full colonoscopy and chest, abdomen, and pelvis CT imaging. If the imaging study results are normal, repeat CT scans are recommended every 3 months until either recurrent disease is identified, or CEA levels stabilize or decline. A PET/CT scan may be useful in this scenario, although the probability of detecting a recurrence not present on a high quality CT scan is low.

Management of Local Recurrence

Despite marked improvements in the local control of rectal cancer with multimodality therapy, locoregional recurrence following surgery remains a challenging problem. Left untreated, patients with pelvic recurrence have a median survival of 8 months and often experience poor quality of life with severe pain and intractable symptoms [35]. Specific advances in multimodality therapy can now allow for cure in selected patients and these cases should be referred to high-volume experienced centers, where developed multi-disciplinary protocols are available, before they are considered unresectable [34–36]. In selected cases an R0 resection with curative intent of a locoregional recurrence is possible and the issues pertaining to the management and outcome of these patients is considered in Chaps. 27, 28 and 29.

Quality of Life

Health-related quality of life (HRQOL) is the extent to which a patient's usual or expected physical, emotional, and social well-being are affected by medical conditions [37]. Similar to other areas of medicine, there has been a shift of focus from exclusively assessing objective oncologic outcomes such as overall and disease-free

survival to subjective and patient-reported outcomes of HRQOL [38]. As a consequence, HRQOL has become an important outcome in clinical trials for rectal cancer. Although the research literature on this topic is growing, the reported findings are often limited, due to the lack of high quality data. Ideally, HRQOL studies should be prospective and longitudinal, with both baseline and post-treatment assessments, using validated HRQOL instruments. Also these studies should be of adequate sample size and power to detect meaningful differences. Unfortunately, few studies, especially in rectal cancer, satisfy these criteria [38–40].

Psychosocial Issues

Generally as might be expected, cancer survivors report greater psychological distress than individuals without a prior history of cancer [41]. This issue is complex and includes fear of recurrence and death, adjustment to physical changes, alterations in customary social support, social reintegration and employment and insurance problems. Distress levels tend to be the highest in the early period following therapy and can be debilitating interfering with everyday life. For colorectal cancer patients specifically, a prospective population-based Australian study by Lynch et al. [42] revealed that 7% of survivors experience clinically significant psychological distress at 1 year post-diagnosis. Women, patients with multiple comorbid conditions and those who lack social support are especially susceptible to depression or psychological distress [42, 43]. In this regard, higher rates of depression persist even among colorectal cancer patients who survive more than 5 years beyond their diagnosis [44].

Assimilating back into work along with social relationships can be difficult for many rectal cancer survivors and they face a higher risk for unemployment when compared with age- and gender-matched healthy adults (54% versus 43%) [45]. While most employed patients with non-metastatic colorectal cancer return to work, approximately one sixth of these patients ultimately leave the workforce [46]. Lower socioeconomic status and advanced age among survivors are associated with significantly higher rates of labor force departure, highlighting the need for directed attention towards this specific subset of the rectal cancer survivor population.

The financial impact of cancer can also result in significant emotional and family stress and may impair HRQOL in several aspects. In one survey, over 30% of colorectal cancer patients cut-down on spending for recreational activities, food and clothing to offset their financial burden [47]. The financial consequences are even further amplified among patients who experience a complication following surgery, which occurs in approximately 25% of patients who undergo colorectal cancer resection [48] in some cases even preventing adherence to recommended treatments because of concerns about financial stress. It is important to note the limitations of psychological screening at a single point in time, and the need for regular monitoring in cancer survivors, so as not to miss these issues during survivorship care. There is also a need to more accurately identify cancer patients who might need in-depth

psychosocial and financial assistance from those who will adjust effectively with their own personal resources and standard health-care services, early on in the cancer care continuum.

Bowel Dysfunction

Up to 60% of rectal cancer patients undergoing low anterior resection (LAR) suffer from bowel dysfunction [49], especially when surgery is combined with radiation therapy [50]. These patients often report a constellation of troublesome symptoms including a median of 3 bowel movements per day, stool clustering, frequency, urgency, emptying difficulties and an inability to differentiate stool from gas. These symptoms are collectively referred to as the LAR (Low Anterior Resection) syndrome. Symptoms often start immediately after surgery and may decrease after a few months, typically reaching a plateau within the first 2 years. Some patients recover almost completely, but others suffer lifelong disability with a major impact on HRQOL [51]. For some the impact is substantial and some patients may withdraw from social and regular daily activities because of the fear of having an accident in public and become socially isolated.

Given the prevalence of bowel dysfunction and its impact on HRQOL in rectal cancer survivors, physicians involved in the survivorship care plan should have an accurate understanding of the symptoms, so that patients are appropriately monitored and managed. Because cancer survivors may prioritize assessments of their oncologic status, above their functional status, during surveillance visits, providers involved in survivorship care for patients with treated rectal cancer will need to specifically inquire about and address defecatory dysfunction. Some patients may assume that poor bowel function is an inevitable and unfixable consequence of treatment and may not discuss these persistent symptoms of their own accord.

In order to facilitate assessments of post-LAR defecatory dysfunction, a concise internationally validated scoring instrument, the LARS score, has been developed (Table 31.3) [49, 52]. The score has high sensitivity and specificity for identifying patients with major bowel dysfunction that degrades HRQOL. Owing to its simplicity and ease of application, the score may be used as a routine screening tool for bowel dysfunction during follow-up. These scores have been validated internationally [53] with the recent use of a preoperative nomogram score (the POLARS) which may clinically predict those patients most likely to encounter postoperative LARS [54].

Management of bowel dysfunction typically includes anti-diarrheal medications, bulk-forming agents, and the use of undergarment pads. Dietary manipulations and the elimination of specific foods (e.g., dairy products, fats and oils, raw vegetables, or fibrous foods) and the use of probiotic supplements are largely controversial or of limited benefit [55, 56]. This issue is covered in greater detail in Chap. 15.

Table 31.3 LARS score questionnaire

Question	Score
Do you ever have occasions when you cannot control your flatus (wind)?	
No, never	0
Yes, less than once per week	4
Yes, at least once per week	7
Do you ever have any accidental leakage of liquid stool?	
No, never	0
Yes, less than once per week	3
Yes, at least once per week	3
How often do you open your bowels?	
More than 7 times per day (24 h)	4
4–7 times per day (24 h)	2
1–3 times per day (24 h)	0
Less than once per day (24 h)	5
Do you ever have to open your bowels within 1 h of the last bowel opening?	
No, never	0
Yes, less than once per week	9
Yes, at least once per week	11
Do you ever have such a strong urge to open your bowel that you have to rush to the toilet?	
No, never	0
Yes, less than once per week	11
Yes, at least once per week	16

Add the scores from each of the five answers to one final score
Interpretation: 0–20 = No LARS | 21–29 = Minor LARS | 30–42 = Major LARS

Living with a Stoma

As part of their surgical management, a significant number of rectal cancer patients require diversion of the fecal stream in the form of either a permanent or temporary stoma. Having a stoma can negatively affect one's daily life and reduce overall functioning and HRQOL. An individual patient's response and subsequent adjustment to having a stoma can be highly variable, thus making management, follow-up care and research very challenging [57]. Ostomates are more likely to experience issues with their self-image, comfort with travel and other physical activities and with their interpersonal relationships. These issues can contribute to higher rates of depression and decreased HRQOL [58]. A recent Cochrane review challenged the notion that patients with a stoma have lower HRQOL [58], although a firm conclusion was not possible due to the large heterogeneity of the included studies. Large well-designed and executed prospective studies are certainly needed to identify optimal approaches to maximizing HRQOL specifically in ostomate rectal cancer survivors.

Sexual Dysfunction

Up to 35% of rectal cancer survivors will experience long-term sexual dysfunction after rectal cancer resections [59]. For men, symptoms include decreased libido, erectile dysfunction and retrograde ejaculation whereas for women, decreased libido or sexual desire, dyspareunia and changes in genital arousal and lubrication are commonly reported [60]. Despite the improvement in surgical techniques and efforts to minimize injury to autonomic nerves, the high prevalence of sexual dysfunction among rectal cancer survivors warrants an increased effort to discuss these issues before treatment. In one study, only 9% of women and 39% of men remember discussing sexual effects of rectal cancer treatment preoperatively [60]. Other studies have also shown that the sexual outcomes following surgery are commonly not included in the informed consent process and moreover that sexual dysfunction is often not sufficiently addressed during the follow-up care. Most patients do not get treatment for sexual dysfunction [60], although a number of therapies are available to address sexual dysfunction in men. In this respect, Sildenafil (Viagra) is highly effective with a 79% response rate for erectile dysfunction following rectal excisions [61], and it should be first-line therapy for these patients. Testosterone replacement therapy may also be effective in increasing sexual desire and may improve erectile function in patients with low levels of serum testosterone.

For women, the treatment options for sexual dysfunction are currently limited. Water- or silicone-based lubricants and vaginal moisturizers can be useful for women experiencing vaginal dryness or dyspareunia. Low-dose vaginal estrogen preparations may also be considered if lubricants alone do not suffice. Pelvic floor muscle retraining and vaginal dilators may be recommended after pelvic radiation therapy to prevent vaginal stenosis, but there are few data to support the efficacy of these approaches. Regular vaginal dilatation may of course be a necessary part of management following more extended posterior vaginectomy. Patients with a stoma also frequently express concerns regarding the psychological aspects of sexual activity, including their partner's response to intimacy. This emphasizes the need for appropriate counseling and support for stoma patients and their partners. Many survivors and their partners also purchase customized undergarments to secure the stoma appliance during intercourse.

Pelvic Fractures

Bone damage and risk of fractures may be increased after pelvic radiation, as a result of radiation injury to the bony microcirculation. Data from a large retrospective study of older women diagnosed with anal, cervical, or rectal cancer has demonstrated a 65% increase in the cumulative incidence of pelvic fractures (most commonly hip fractures) in rectal cancer survivors who had received pelvic radiation [62]. With improvements in modern radiation techniques, there is evidence that

pelvic fractures are encountered less frequently after therapy [50]. As rectal cancer survivors are often older or have multiple comorbidities, they may have other additive risks for bone density loss and therefore should receive appropriate monitoring of bone mineral density, timely management of osteopenia and osteoporosis and careful evaluation when symptoms suggesting a fracture are volunteered.

Peripheral Neuropathy

Oxaliplatin-induced peripheral neuropathy has become a common and occasionally a dose-limiting toxicity during adjuvant therapy. It most frequently manifests as sensory impairment in a glove and stocking distribution. Numbness, cold-induced pain, dysesthesia, and changes in proprioception may affect fine motor skills, such as buttoning shirts or holding a pen. Symptoms mostly appear after Oxaliplatin cumulative doses exceeding 780 mg/m^2 and are thought to be due to the accumulation of the drug metabolite oxalate within the dorsal root ganglia [63]. Up to 92% of patients treated with Oxaliplatin develop some degree of sensory neuropathy and 10% have neuropathy severe enough that it interferes with daily functioning. Symptoms are mostly in the hands during therapy, but persistent symptoms are frequently reported in the feet [63]. The majority of patients, fortunately adapt or have subjective improvement in nerve function and about 50% of survivors recover within 9 months of discontinuation of treatment. Despite this, however, up to 12% may complain of long-term persistent numbness or pain [56, 63].

Lifestyle Modification

Cancer survivors are often motivated to make healthier lifestyle choices and to seek information about physical activity, diet and dietary supplements [64]. This proves to be a unique opportunity to implement primary, secondary and tertiary preventative strategies and lifestyle modifications that may result in improved HRQOL, general health and even better cancer survival. Cancer survivors, who adopt these changes, often maintain these healthy behaviors over the long-term.

In this respect, increased physical activity has been shown to improve overall health and HRQOL, to lower cancer incidence rates and also to lengthen cancer survival [65]. In a prospective observational study of stage III colon cancer survivors, Meyerhardt and colleagues [66] demonstrated a 47% disease-free survival benefit in survivors who engaged in at least 18 MET-hours per week of physical activity (6 or more hours per week of walking at an average pace). It may be argued in this instance, that colorectal cancer survivors can be limited in their ability to exercise, however, several studies have shown that their physical functioning and recreational activities at 1 year following therapy are nearly identical in comparison with those without a cancer diagnosis [66].

Survivors will often ask what foods they should eat or avoid. While most of the data are observational in this regard, it does suggest that a Western diet, which is characterized by higher intakes of red and processed meats, sweets and desserts, fried food and refined grains, increases the risk of colon cancer recurrence and decreases overall survival, when compared with a diet characterized by high intakes of fruits and vegetables, poultry and fish [67]. Data from the Cancer Prevention Study II Nutrition Cohort suggests colorectal cancer survivors who have consistently high red or processed meat intake before and after diagnosis had a higher risk of cancer-specific mortality (Relative risk = 1.79; 95% confidence interval = 1.11–2.89) [68].

Survivors should also be counseled about the importance of weight control, which may reduce the risk of cancer recurrence and improve overall health status. Obesity in male patients with rectal cancer is associated with higher local recurrence rates [69]. Although most studies examine weight and BMI prior to therapy, the overall benefits of weight control can be extrapolated to the rectal cancer survivor.

Every opportunity to improve other general lifestyle behaviors, such as smoking cessation, should be taken, as these interventions are likely to improve overall health in a potentially receptive survivor who is open to behavior change [70]. Every 5 years, the American Cancer Society publishes an extensive list of lifestyle characteristics that promote general health at the patient- and community-level, and which may potentially translate into decreased risks of rectal cancer recurrence [71]. Discussing these lifestyle behaviors may encourage patients to make choices and changes towards a healthier lifestyle.

Coordination of Care

Over 70% of all cancer survivors have comorbid conditions and the majority report at least one persistent symptom attributable to their cancer diagnosis or treatment [56]. Healthcare during the survivorship period should be inclusive and comprehensive, to include general health, comorbidities, cancer-specific issues and the aforementioned HRQOL effects of treatment. However, this phase is often viewed as the "weakest link" in cancer care [72]. Thus, several survivorship healthcare models have been proposed, in essence where all models are centered on the coordination of care to provide comprehensive and tailored follow-up [73].

Before discussing the coordinated models of survivorship care, it is important to highlight the stakeholders' perspectives and the deficiencies in usual follow-up care. In one survey of 431 cancer survivors, 123 oncologists and 255 primary care physicians, Cheung and colleagues [74] found that survivors expect their oncologists, primary care physicians, or both to be responsible for their care and moreover, that oncologists primarily want to have a role in cancer-related care with primary care physicians expecting to be involved in essentially all domains of cancer survivorship care. This lack of clarity in the relative roles that primary care and specialist physicians play, may consequently lead to deficiencies in recommended care as well as duplicated services and costs.

Several studies have shown that when compared with adults without a cancer diagnosis, colorectal cancer survivors are less likely to receive appropriate follow-up for heart failure, necessary diabetic care, recommended preventive services, and health behavioral counseling [75, 76]. These deficiencies are ameliorated when both primary care physicians and specialists are involved in follow-up [75]. When survivors are followed up by a single specialty, however, the care rendered readily becomes unbalanced.

In general, colorectal cancer survivors who are followed by primary care physicians alone tend to receive more preventive services and appropriate management for comorbid conditions than do patients who are seen by specialists alone. Even though colorectal cancer survivors do not perceive differences in the quality of care rendered between primary care providers and specialists [77], most primary care providers are actually unfamiliar or uncertain about surveillance protocols and long-term side effects of treatments [78]. Less than 10% of colorectal cancer survivors receive recommended surveillance when not in the care of an oncologist [18] and importantly, primary care providers frequently report dissatisfaction with the transfer of care from specialists.

The shared care model may be the optimal model for rectal cancer survivorship care and it is supported by the Institute of Medicine. In this model, the roles and responsibilities for survivorship care are well delineated for both patients and their providers. Coordinated care between the primary care physician and the specialist would optimize adherence to guidelines for recommended follow-up cancer survivors and also optimize the management of comorbid conditions. In order to accomplish this, a Survivorship Care Plan, such as that developed by the American Society of Clinical Oncologists [79], and endorsed by the American College of Surgeons Commission on Cancer is warranted [80]. Ideally, the plan is to be completed at the end of primary therapy by the specialist providers and should include a summary of the neoadjuvant or adjuvant therapy received, a description of the surgical procedure, the plan for surveillance of cancer recurrence, the anticipated complications of therapy, ways to address the chronic physical and psychosocial effects of cancer and necessary lifestyle and preventive care measures appropriate for the individual survivor. Survivorship care quality metrics will soon become requirements in cancer center accreditation. Rigorous qualitative, observational and interventional research will then be needed in order to address whether enforcing and implementing these measures will directly be responsible for better survivorship care, patient and provider satisfaction, and ultimately better overall cancer survival.

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Part XI
An Economic Analysis of Modern Rectal Cancer Care

Chapter 32
The Economics of Rectal Cancer Care: Considerations in Interpretation of the Literature

Andrew P. Zbar and Nir Horesh

This chapter provides a general overview of considerations when economic analyses are reported for the management of patients with rectal cancer. Although we have included an assessment of selected European, Australasian and North American variations in reported series as they pertain to rectal cancer for the use of radiotherapy, adjuvant-neoadjuvant chemotherapy and multimodality therapy, we describe more the pitfalls in the interpretation of comparative economic data assessing rectal cancer care.

There are many ways to comparatively assess the costs of care in a condition like rectal cancer. Some analyses might focus on the performance characteristics of the delivery of quality cancer care across different systems, whereas others concentrate on cancer-specific outcomes such as survival. Economic analyses might also assess the cost or the cost-effectiveness of rectal cancer prevention with an emphasis in developed environments where there are reliable cancer registries of either population-level assessments (assessing the performance within and between health systems) or patient-level analyses (designed to investigate the effectiveness of programs for individual patient care). The former might use instruments such as cancer mortalities or cancer-specific survival whereas the latter determine the value of initiated anticancer systems [1].

In 2008, there were an estimated 2.1 million patients diagnosed with colorectal cancer (CRC) worldwide [2] two-thirds of whom lived in developed countries. The comparative national data have improved over recent years because of the organization of cancer incidence teams examining data on cross-national CRC incidence,

A. P. Zbar (✉)
Department of Surgery and Transplantation, Department of Surgery B, Chaim Sheba Medical Center, Tel Hashomer Hospital, Ramat Gan, Israel

Department of Anatomy and Neuroscience, The University of Melbourne, Parkville, VIC, Australia

N. Horesh
Department of Surgery and Transplantation, Chaim Sheba Medical Center, Ramat Gan, Israel

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mortality and survival. Such agencies include the International Agency for Research on Cancer (IARC), (an offshoot of the World Health Organization), the European Cancer Registry (EUROCARE) and its own offshoot CONCORD which examines survival estimates for a range of cancers including breast, colon, rectum and prostate [3]. The Organization for Economic Cooperation and Development (the OECD) compiles information concerning the economic expenditure by countries but does not produce cross-national expenditure assessments on individual cancers [4]. In theory at least, comparisons of regional performance in quality cancer care delivery are possible, potentially providing information concerning both the quality and the value of existent practices. Such an analysis by Gigli and colleagues [5] found clear differences in approach between the United States and Italy for example in the utilization of adjuvant therapies in CRC as well as in the use of abdominal surgery, endoscopy and hospitalization. More developed environments with well kept registries can determine the impact of guideline recommendations by cancer societies of screening modalities, imaging systems during follow-up and the use of specialized radiotherapy protocols [6]. Rectal cancer is particularly complex in comparing its economic impact where indirect costs and the effects on productivity induced by the disease and its treatment for example are frequently not measured [7, 8].

Moreover, the current systems of analysis of data (insurance and administrative data systems, hardcopy and electronic medical records and registry databases), have not been designed for research and much data as it pertains to the economics of rectal cancer care can only be inferred from economic modeling derived from other non-cancer sources. Even if the tools to assess the costs incurred by rectal cancer patients are currently inadequate, there is a recognition that with an increase in cancer incidence (with increasing age as part of an overall ageing population with access to technologies designed to detect more and earlier tumors), that there will be significant increases in rectal cancer health expenditure [9–11]. Given the diversity of health care delivery systems and their financing, these issues along with the increased expense of novel effective chemotherapeutic and immunotherapeutic drugs on rectal cancer care will significantly impact the future decisions of health care policy makers [12]. Concerning this latter point, the spending on cancer drugs has risen faster than almost any other area of cancer care increasing in the United States from $3 Billion in 1997 to $11 billion by 2004 (an increase of 267%). This figure can be compared with the total Medicare bill rise during that same period ($210 billion to $309 billion; 47%) [13, 14]. In this environment, the rising cost of these new drugs outstrips in some cases their economic benefit placing patients at serious personal financial risk from out of pocket expenses and this should be keyed in to the fact that cancer survivors (particularly the non-elderly) have been shown to change their prescription use over time entirely for financial reasons [15]. This impression of less of an economic cost-effectiveness (where the magnitude of the increase in drug cost has exceeded the magnitude of the improvement in efficacy), has been expressed for the range of new drugs on offer for patients with hepatic colorectal metastases [16].

Table 32.1 shows the comparative overall cancer incidence, mortality rates and survival across the major OECD countries [16, 17]. This data shows considerable

Table 32.1 Cancer demographics and expenditure by health care system

Statistic	USA	UK	Canada	OECD (mean)[a]
Cancer incidence (rate per 100,000 persons)	300.2	269.4	296.6	260.9
CRC 5-year OS	64.5	53.3	63.4	59.9
Mortality per 100,000 persons				
Females	130	141	143	124
Males	185	199	205	208
Mean LOHS	4.9	7.7	7.7	7.1
Mean CT scans per 1000	265	76.4	126.9	123.8
Health care spending per capita ($)	8233	3433	4445	3265
% Public expenditure (Health)	48.2	83.2	71.1	72.2

After Yabroff et al. [17]
OS overall survival, *LOHS* length of hospital stay (days), $ USD adjusted
[a]Based on a selection of 34 OECD countries

variation across the participating countries in the average length of hospital stay, the use of diagnostic imaging, the mean cancer mortality rates and in per capita national health-care expenditure [18]. Comparisons between these countries are fraught with problems where there are inherent differences in the percentage of public expenditure on health, the administrative costs and negotiated hospital, physician and pharmaceutical awards [19]. This is not to imply that the assessment of this data is overly limited, however, as it will provide direction within specific health care systems on what may be regarded as best practice management of rectal cancer [20] as well as the higher value outcomes which can influence all aspects of care including screening, treatment and end-of-life care.

The pattern of cancer care directly affects outcomes and costs which reflect unit decisions concerning initial surgery, chemotherapy (CT), radiotherapy (RT), surveillance programs following initial treatment and end-of-life care. The origin of data acquisition is also important where for example SEER Medicare US studies are only applicable to patients >65 years of age. Equally, hospital –acquired data do not reflect many aspects of diagnosis or longitudinal information about care. For rectal cancer management, such data may not adequately reflect trend changes in neoadjuvant therapy or sphincter-sparing surgery. Costing analyses will also need to distinguish between what Yabroff et al. calls direct medical and non-medical costs [21]. The former represent those incurred with inpatient and outpatient care and with ambulatory services as well as those involved in surgery, CT and RT delivery. The latter include the economic effects of patient transport, care giver costs and the like. Further indirect or productivity costs need to be considered from a social point of view affecting loss of time from work, impaired work status and the economic impact of severe restrictive morbidity or mortality.

Table 32.2 shows the reported European (and Australasian Commonwealth) and North American rates of surgical treatment for rectal cancer which reveals that there is currently considerable variability in resection rates. This issue is complex, however, as variability reflects differences in population age, gender, socioeconomic status, co-morbidity registration and geographical location [22–45]. There is in this data a general reduction in the incidence of institutional abdominoperineal resection

Table 32.2 Geographic patterns of care for the initial surgical treatment of rectal cancer

Author (Year) [Ref]	Country	Recruitment	Number	Outcome
Elferink 2010 [22]	Netherlands	1989–2006	40,888	Stable RR <75
	CR			Reduced RR in elderly (91–81%)
				Stage IV young pts had Mx
Khani 2010 [23]	Sweden	1993–6	277	38% AR, 8% LAR, 38% APR
		1996–9		3% AR, 55% LAR, 18% APR
Marwan 2010ß [24]	Australia	2005	582	23%APR, 53% AR, 23% ULAR
Raine 2010 [25]	UK	1998–2006	29,214	72% AR, more common in women and elderly
Martling 2009 [26]	Sweden	1995–2002	11,774	52%AR, 27% APR, 10% HOP
Sigurdsson 2009 [27]	Norway	1997–2002	297	64% noncurative Sx; 48% stoma rate
Tilney 2008 [28]	UK	1996–2004	52,643	25% APR, (decreased to 21.2%)
Ptok 2007 [29]	Germany	2000–1	1557	APR rate correlated with volume
Phelip 2004 [30]	France	1990/1995	945	RR increased from 84.6–91.9%
Wibe 2004 [31]	Norway	1993–9	2136	62% AR, 38% APR
Engel 2003¶ [32]	Netherlands	1994–9	15,978	16% APR, 84% RR ¥
Farmer 2002ß [33]	Australia	1994	681	AR 63%, 24$ APR, LE 5%
Garcia-Granera 2001 [34]	Spain	1986–95	202	APR rate reduced 26–17%
Young 2007 [35]	Australia	2000–1	2984	29% LAR had a CP
Lemmens 2006 Ω [36]	Netherlands	2002	308	55% LAR, 37% APR; 5% HOP; 89% RCI
Hall 2005 [37]	Australia	1982–2001	14,587	85.5% RR; 41% AR
Jestin 2004 [38]	Sweden	1995–2000	3612	51% LAR; 25% APR; 1.2% HOP
Chiappa 2001 [39]	Italy	1992–9	346	74% RCI
Pisu 2010 [40]	USA	1999–2003	675	90% RR
Latosinsky 2009 [41]	Canada	1984–97	333	47% AR; 51% APR; 2% HOP
Chang 2007 [42]	USA	1991–2002	21,390	15% LE; 44%LAR; 26% APR
Ricciardi 2007 [43]	USA	1998–2003	117,773	% SSS increased 27–48%
Phang 2003 [44]	Canada	1996	481	51% AR; 33% APR; 5% HOP
Schroen 2001 [45]	USA	1994–6	637	93% RR; 55% APR

Tables combined data from: Chawla et al. [7] and Butler et al. [8]
RR resection rate, *Mx* metastasectomy, *CR* cancer registry, *AR* anterior resection, *LAR* low anterior resection, *ULAR* ultralow anterior resection, *HOP* hartmann's operation, *Sx* surgery, *RCI* resection with curative intent, *CP* colonic pouch, *LE* local excision, *SSS* sphincter sparing surgery, *NR* not recorded, ¶ Dutch National Registry dBase, ¥ APR rate did not decrease over time in University hospitals but did decrease in non-University hospitals, Ω Eindhoven Cancer Registry, ß Victorian Cancer Registry

(APR) with increasing novel sphincter-sparing surgeries [28, 29]. Younger patients and those in a higher socioeconomic bracket are more likely to be resected [46] with older more co-morbid metastatic cases less likely to receive surgical treatment. These patient-related demographics (such as the level of private care and the presentation of the rectal cancer to an emergency room) combine with hospital

demographics (the volume of rectal cancer cases) to affect presentation, management and overall cost [37, 47, 48].

With the increasing use of preoperative RT and neoadjuvant chemoradiotherapy in rectal cancer (Stage III and some high-risk Stage II cases with extramural venous invasion on MR imaging), there has been an assessment of the economic impacts of ancillary treatments. The true economic cost in this changing environment may need to reflect new intensity modulated therapies and even contact brachytherapy in early cases in the context of trials (such as the OPERA trial comparing external with contact beam RT in low T2 and T3a-b tumours; NCT02505750) and the added costs of patient recruitment and transport where specialized facilities are only available at particular sites. Sweden was the first to utilize preoperative short-course RT in a concerted trial and where there are detailed analyses of RT implementation. This approach has been followed by the Netherlands and also Norway with recording of the rates of RT use (Table 32.3) [22, 26, 30, 31, 33, 35, 40, 41, 44, 45, 48–61]. Similarly to chemotherapy there are demographic reasons for low pick-up rates of RT amongst identifiable groups such as the elderly including some cases of more advanced stage disease or for palliative use. The change in philosophy towards preoperative over postoperative RT use (in terms of better locoregional recurrence rates) has seen over time in most countries the decline of postoperative schedule use. This was cemented into practice after reports of the Uppsala trial which has been highlighted in this book [62]. In the Netherlands for example the percentage of rectal cancer patients receiving RT increased from 47% during 1998–2002 up to 63% (2003–2006) with a steady decline in postoperative RT since 1995 when preoperative RT was introduced [49]. This change was induced by the national introduction of short-course adjuvant therapy in patients with clinically resectable rectal cancer and also participation in the Dutch TME trial which ran between 1996 and 2000 [63]. Despite widespread implementation and a slight dip in use in 2004 (most likely a result of publication of the side-effects of long-course therapy), the take-up rate in elderly patients with rectal cancer still remains comparatively low; an effect also noted in other RT population-based studies [64]. The data here are conflicting since those patients with operable rectal cancer submitted to TME have a reduced locoregional recurrence rate (LRR) although without an increase in either overall survival (OS) or disease-free survival (DFS) when preoperative short-course RT is used. In this group delaying surgery and assessing a greater level of pathologic complete response (pCR) and near pCR may obviate the increased incidence of postoperative complications in older cases [65, 66]. Similar findings have been noted by the French group reported by Faivre-Finn et al. [53] where there is underutilization of RT in patients >75 years of age by approximately one-third.

Clearly the types of rectal cancers included within these studies will affect the results, where later-staged, more advanced cases are more likely to receive preoperative RT, also reflecting hospital volume and surgical type. The trend to use less RT in women where surgery has been more relied upon has also been reported. Overall, the results for RT use in the USA and Canada are similar although data are obtained in the US from Surveillance Epidemiology and End Results (SEER) and from Medicare RT Claims. Including the standard groups (Stage II/III) the use of

Table 32.3 Geographic patterns of care for the radiotherapeutic treatment of rectal cancer

Author (Year) [Ref]	Country	Recruitment	Number	Outcome
Elferink (2010) [22]	Netherlands	1989–2006	40,888	Stage II/III Preop RT
				1% (1988) to 68% (2004)
				Postop RT reduced: 46% to 4%
Martling (2009) [26]	Sweden	1995–2002	11,774	46.5% Preop RT
				Less women than men (42.5% vs. 50.1%)
Vulto (2009) [49]	Netherlands	1998–2006	7767	47% RT (1998–2002); 63% (2003–6)
Hansen (2007) [50]	Norway	1993–2001	4113	6.9% Preop RT vs. 5.6% postop RT
				Overall 4.6% (1994) to 23% (2001)
Ng (2006) [51]	UK	1995–9	207	36.2% of operated cases
Phelip (2004) [30]	France	1990/1995	683	42% RT (1990) 47% (1995)
Wibe (2004) [31]	Norway	1993–9	2136	10% RT; 6% Preop, 4% postop
Birbeck (2002) [52]	UK	1986–97	586	4.3% Preop RT
Farmer (2002) [33]	Australia	1994	681	74.5% with surgery; 4.4% Preop
Faivre-Finn (2000) [53]	France	1976–96	651	37.3% resected cases 14.3% (1976–8)
				61.7% (1994–6)
Gatta (2010) [48]	ECS*	1996–8	6871	12% stage I–III
Carsin (2008) [54]	Ireland	1994–2002	15,249	Increased by 10% per annum
Coriat (2007) [55]	France	1998	407	43% postop RT
Young (2007) [35]	Australia	2000–1	2984	59.8% operated cases
McGrath (2004) [56]	Australia	2000	1911	65.6% locally advanced
				76.3% non-operated cases
Kuo (2010) [57]	USA	1994–2003	329	54% of all cases; 71% postop RT
Lin (2010) [58]	USA	1998–2005	8978	31% Preop RT; 37% postop RT
Pisu (2010) [40]	USA	1999–2003	675	15% Preop RT, 25% adjuvant RT
Latosinsky (2009) [41]	Canada	1984–97	333	47% adjuvant RT; 1% Preop RT
Demers (2008) [59]	Canada	1985–99	2925	Increase 32% to 45%
Dobie (2008) [60]	USA	1992–9	2886	55% of all cases; 48% St II, 62% St III
Baxter (2006) [61]	USA	1976–2005	> 18,100	Overall 32% of cases; increase 15% to 42%
Phang (2002) [44]	Canada	1996	481	60% St II/III; 89% as Preop RT
Shroen (2001) [45]	USA	1994–6	637	14% St I, 53% St II, 63% St III, 30% St IV

Table modified from data acquired from Chawla et al. [7] and Butler et al. [8]
*European Collaborative Study

RT increased in the United States from an average of 15% in 1970 to 50% in the first decade of the twenty-first century [8, 59].

Table 32.4 shows some studies assessing CT use in rectal cancer which also vary widely in the major OECD countries depending upon the tumour stage and

Table 32.4 Geographic patterns of care for the chemotherapeutic treatment of rectal cancer

Author (Year) [Ref]	Country	Recruitment	Number	Outcome
Elferink (2010) [22]	Netherlands	1989–2006	40,888	Stage IV increased 21–66% in young vs. 2–25% in elderly
Phelip (2004) [30]	France	1990, 1995	945	Adjuvant CT rose 8.1% to 19%
				Palliative CT rose 37.5% to 50% in pts <75 years
Martijn (2003) [64]	Netherlands	1980–2000	3635	CT use increased 0–10% stage III
				7–30% stage IV
Gatta (2010) [48][a]	European collaborative	1996–8	6871	Stage II increased 22% (38% <65 years vs. 5% >75 years)
Carsin (2008) [54][a]	Ireland	1994–2002	15,249	CT use increased 10% per annum for all stages, 31% overall
Damianovich (2007) [67][a]	Australia	2002–3	1465	Oxaliplatin increase 48–66%
				Irinotecan decrease 52–34%
Robinson (2005) [68][a]	New Zealand	1993–4 and 1989–99	673	Adjuvant CT increase for dukes C 21–45%
				Metastatic disease 2.4–23% increase
Kuo (2010) [57]	USA	1994–2003	329	45% stage II cases received CT
Pisu (2010) [40]	USA	1999–2003	675	11% received neoadjuvant, 37% adjuvant
Romanus (2009) [69]	USA	2005–8	2042	81% stage II/III <80 years
Demers (2008) [59]	Canada	1985–1999	2925	CT increase 13–37%
Dobie (2008) [60]	USA	1992–9	2886	52% received CT overall, 42% stage II, 63% stage III
Schroen (2001) [45]	USA	1994–6	637	11% stage I, 54% stage II
				70% stage III, 55% stage IV

Table modified from data acquired from Chawla et al. [7] and Butler et al. [8]
[a]Rectal cases included in assessment studies labeled as 'Colorectal'

principally upon patient age [22, 30, 40, 45, 48, 54, 57, 59, 60, 64, 67–69]. In brief summary, the trend has been for increased CT use over time with old age a barrier to use and with a significant survival impact. This effect is extended out to a reduced CT use in some studies in women and those of lower socioeconomic status. Specifically for rectal cancer, the impact of hospital (University *vs.* rural District General Hospital), hospital volume and if a presentation is emergency (ER) in type, all need further cost evaluations [70–73]. Finally, as a discrete management principle, there has been little assessment of multimodal care and its economic impact

particularly over different management regions, with some data emerging from the Netherlands, Germany, Australia, Italy and the United Kingdom. These data are difficult to compare because of inherent differences in stratification for patient stage, age and date of diagnosis as well as for the registry source of assessable data. Table 32.5 shows some comparative data for the implementation of multi-component therapy in Europe (and Australasia) and North America [22, 27, 29, 33, 40, 41, 59, 60, 72, 74, 75]. The trend has largely shown higher rates of neoadjuvant therapy use over time most notably in younger, fitter patients and in large volume hospitals. Specifically in the USA, where much of the data was obtained from HMO insurance networks rather than by specialized groups (such as the National Comprehensive Cancer Network – NCCN), there was a lower use of CT among patients with only Medicaid coverage as well as those with pre-existent co-morbidities. This effect extended to race where black populations with a similar level of specialist oncology referral tended to receive CT less often [76, 77].

In summary, rectal cancer is an expensive disease. Both targeted therapy and a shift towards selected organ preservation will create new add-on costs. Cost analyses need to incorporate underestimated costs of care which are dependent upon the phase of assessment where there is a "U-shaped" cost curve presenting with the highest cost profile at initial registration of patients and in their final phase [78]. The latter represents the high cost of short survivors, principally in diagnostics, the need for late surgical procedures and the economic effects of terminal care. These costs may be improved for predictable areas by the use of projection tools which evaluate

Table 32.5 Geographic patterns of multimodality care for the treatment of rectal cancer

Author (Year) [Ref]	Country	Recruitment	Number	Outcome
Elferink (2010) [22]	Netherlands	1989–2006	40,888	Neoadjuvant increases in young stage II from 1–9%
				Elderly St II/III were <3%
Sigurdsson (2009) [27]	Norway	1997–2002	297	10% combination CT + RT
Ptok (2007) [29]	Germany	2000–1	1557	Neoadjuvant increase 6.5–25%
				(2000 *vs.* 2005)
Farmer (2002) [33]	Australia	1994	681	CT + RT in 65.3%
Kube (2009) [74]	Germany	2000–5	346	Neoadjuvant increase from 6.5–25%
Lemmens (2005) [72]	Netherlands	1995–2001	6931	Adjuvant for stage II/III increased from 3.9% (1995–9) to 15.9% (2001)
Pisu (2010) [40]	USA	1999–2003	675	17% overall received CRT
Lasotinsky (2009) [41]	Canada	1984–97	333	Concomitant CT with RT in 80%
Demers (2008) [59]	Canada	1985–1999	2925	Perioperative CRT increased from 1% to 25%
Dobie (2008) [60]	USA	1992–9	2886	38% stage II CRT, 54% stage III
Cronin (2006) [75]	USA	2000	352	>half patients stage II/III were treated with CRT according to guidelines

Table modified from data acquired from Chawla et al. [7] and Butler et al. [8]

the impact of specific health interventions [79]. The aggregate cancer burden in any given population is the type of data required in order to assess a national expenditure but even this will not necessarily predict for microlevel costs and for future as yet undeveloped interventions and health policies. Our chapter has focused on disparities in the reported data concerning adjuvant and neoadjuvant therapies and ignores the costs involved in cancer control measures, screening programmes, early diagnostic testing, stoma-related costs, the costing of new minimally invasive strategies and the impact of hospital readmission during continuing treatment. The big ongoing and future economic questions in rectal cancer care will include the downstream cost-benefit of cancer prevention and screening, the high cost of targeted treatments and tumour genomic assessment, the implementation of consensus surveillance protocols during survivorship and the costs of strategic interventions in end of life care. Practical strategies for cost sharing of these expensive treatments may require a registration with providers of some sort of managed entry to health coverage [80] even whilst the benefits of some of these new technologies are still somewhat up in the air.

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Index

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